BARAN & DAWBER'S
Diseases of the Nails and their Management

EDITED BY
Robert Baran, David de Berker, Mark Holzberg, Bianca Piraccini, Bertrand Richert, and Luc Thomas

https://t.me/MBS_MedicalBooksStore
Baran & Dawber’s Diseases of the Nails and their Management
Baran & Dawber’s Diseases of the Nails and their Management

Fifth Edition

Edited by

Robert Baran, MD, PhD
Hon. Pr. of the University of Franche-Comté; Nail Disease Centre, Cannes, France

David de Berker, BA, MBBS, MRCP, PhD
Bristol Dermatology Centre, Bristol Royal Infirmary, Bristol, UK

Mark Holzberg, MD, PhD
Department of Dermatology, Emory University School of Medicine, Atlanta, GA, USA

Bianca Maria Piraccini, MD, PhD
Division of Dermatology, Department of Experimental, Diagnostic and Specialty Medicine, University of Bologna, Bologna, Italy

Bertrand Richert, MD, PhD
Department of Dermatology, Brugmann, St Pierre and Queen Fabiola University Hospitals, Université Libre de Bruxelles, Brussels, Belgium

Luc Thomas, MD, PhD
Department of Dermatology, Centre Hospitalier Lyon Sud; Lyon Cancer Research Center (Pr Puisieux); Lyon 1 Claude Bernard University, Lyon, France

WILEY Blackwell
Contents

List of Contributors vii
List of Abbreviations ix
Foreword xi
Preface xiii
About the Companion Website xiv

Part I The Normal Nail and Nail Signs 1

1 Science of the Nail Apparatus 1
   David de Berker, Beth S. Ruben, and Robert Baran

2 Physical Signs 59
   Adam Rubin, Mark Holzberg, and Robert Baran

Part II Imaging of the Nail Unit 105

3 Nail Photography 105
   Paola Pasquali

4 Dermoscopy 113
   Luc Thomas, Sébastien Debarbieux, and Amélie Boespflug

5 Ultrasound and Other Imaging Methods 140
   Ximena Wortsman, Gregor B.E. Jemec, and Axel Villani

6 Magnetic Resonance Imaging 175
   Jean-Luc Drapé

7 Nail Fold Capillary Microscopy or Capillaroscopy 201
   Gregor B.E. Jemec

8 Confocal Microscopy 204
   Sébastien Debarbieux, Amélie Boespflug, Bruno Labeille, and Luc Thomas

Part III Nail Disorders Occurring Principally in Childhood 213

9 Hereditary and Congenital Nail Disorders 213
   Smail Hadj-Rabia, Rudolf Happle, Bianca Maria Piraccini, and Robert Baran

10 Nail Disorders in Childhood 297
    David de Berker, Bianca Maria Piraccini, Beth S. Ruben, and Robert Baran
Part IV  Nail Disorders in the Elderly  337

11  The Aging Nail and Related Disorders  337
   Bertrand Richert

Part V  Nail Infections  349

12  Fungal (Onychomycosis) and Other Infections Involving the Nail Apparatus  349
   Roderick J. Hay, Boni Elewski, Bianca Maria Piraccini, Nikki Sullivan, Casey Wang, and Robert Baran

13  Bacterial, Viral, and Other Infections  390
   Archana Singal and Bertrand Richert

Part VI  The Nail in Dermatological Conditions  409

14  Dermatological Disorders  409
   Bianca Maria Piraccini, Mark Holzberg, Marcel Pasch, and Dimitrios Rigopoulos

Part VII  The Nail in Systemic Conditions  481

15  The Nail in Systemic Disease  481
   Mark Holzberg and Bianca Maria Piraccini

16  Drug-induced Nail Disorders  574
   Bianca Maria Piraccini

17  Anticancer Therapies  604
   Vincent Sibaud, Robert Baran, Bianca Maria Piraccini, Mario E. Lacouture, and Caroline Robert

Part VIII  The Nail in Occupational, Podiatric, and Cosmetic Conditions  617

18  Occupational Abnormalities and Contact Dermatitis  617
   Robert Baran and An Goossens

19  Cosmetics: the Care and Adornment of the Nail  646
   Douglas Schoon and Robert Baran

20  Trauma from Footwear and Pedal Deformities  662
   Bertrand Richert

Part IX  Nail Tumors and Surgery  675

21  Tumors of the Nail Apparatus and Adjacent Tissues  675
   Marcel Pasch, Eckart Haneke, Robert Baran, Luc Thomas, and Bertrand Richert

22  Nail Surgery  825
   Bertrand Richert, Eckart Haneke, Elvin G. Zook, and Robert Baran

Appendix  896
   Mark Holzberg
List of Contributors

Robert Baran, MD, PhD  
Hon. Pr. of the University of Franche-Comté; Nail Disease Centre, Cannes, France

Amélie Boespflug, MD, PhD  
Department of Dermatology, Centre Hospitalier Lyon Sud; Lyon Cancer Research Center (Pr Puisieux); Lyon 1 Claude Bernard University, Lyon, France

Sébastien Debarbieux, MD  
Department of Dermatology, Centre Hospitalier Lyon Sud; Lyon Cancer Research Center (Pr Puisieux); Lyon 1 Claude Bernard University, Lyon, France

David de Berker, BA, MBBS, MRCP, PhD  
Bristol Dermatology Centre, Bristol Royal Infirmary, Bristol, UK

Jean-Luc Drapé, MD, PhD  
Department of Radiology, Hôpital Cochin, University Paris Descartes, Sorbonne Paris Centre, France

Boni Elewski, MD  
Department of Dermatology, The University of Alabama at Birmingham, Birmingham, AL, USA

An Goossens, RPharm, PhD  
Professor Emeritus, Contact Allergy Unit, University Hospital K.U. Leuven, Leuven, Belgium

Smail Hadj-Rabia, MD, PhD  
Department of Dermatology and Reference Center for Genodermatoses and Rare Skin Diseases; University Paris Descartes - Sorbonne Paris Cité; Institut Imagine, Paris, France

Eckart Haneke, MD, PhD  
Department of Dermatology, University of Bern, Bern, Switzerland; Centro de Dermatologia Epidermis, Porto, Portugal; Department of Dermatology, University of Ghent, Ghent, Belgium

Rudolf Happle, MD  
Universitaets-Hautklinik, Freiburg, Germany

Roderick J. Hay, DM, FRCP  
King’s College London, London, UK

Mark Holzberg, MD, PhD  
Department of Dermatology, Emory University School of Medicine, Atlanta, GA, USA

Gregor B.E. Jemec, MD, DMSc  
Department of Dermatology, Zealand University Hospital, Roskilde; Health Sciences Faculty, University of Copenhagen, Copenhagen, Denmark

Bruno Labeille, MD  
Dermatology Department, Hôpital Nord, Saint Etienne, France

Mario E. Lacouture, MD, PhD  
Dermatology Service, Memorial Sloan Kettering Cancer Center, New York, NY, USA

Marcel Pasch, MD, PhD  
Department of Dermatology, Radboud University Medical Center, Nijmegen, The Netherlands

Paola Pasquali, MD  
Pius Hospital de Valls, Tarragona, Spain

Bianca Maria Piraccini, MD, PhD  
Dermatology, Department of Experimental, Diagnostic and Specialty Medicine, University of Bologna, Bologna, Italy

Bertrand Richert, MD, PhD  
Department of Dermatology, Brugmann, St Pierre and Queen Fabiola University Hospitals, Université Libre de Bruxelles, Belgium
List of Contributors

Dimitrios Rigopoulos, MD
National and Kapodistrian University of Athens;
Medical School, University Hospital “A. Sygros”;
Department of Dermatology and Venereology, Athens, Greece

Caroline Robert, MD, PhD
Department of Dermatology, Institut Gustave Roussy, Villejuif; Department of Dermatology, Paris-Sud University, Orsay, France

Beth S. Ruben, MD
Dermatology/Dermatopathology, University of California, San Francisco; Dermatopathology, Palo Alto Medical Foundation, Palo Alto, CA, USA

Adam Rubin, MD
Departments of Dermatology, Pediatrics, and Pathology and Laboratory Medicine, Hospital of the University of Pennsylvania; Children’s Hospital of Philadelphia, Perelman School of Medicine at the University of Pennsylvania, Philadelphia, PA, USA

Archana Singal, MD, MNAMS
Department of Dermatology and STD, University College of Medical Sciences, Delhi, India

Nikki Sullivan, MD
Department of Dermatology, University of Michigan, Ann Arbor, MI, USA

Luc Thomas, MD, PhD
Department of Dermatology, Centre Hospitalier Lyon Sud; Lyon Cancer Research Center (Pr Puisieux); Lyon 1 Claude Bernard University, Lyon, France

Axel Villani, MD
Dermatology Department, Edouard Herriot Hospital, Lyon 1 Claude Bernard University, Lyon, France

Casey Wang, MD
Department of Dermatology, The University of Alabama at Birmingham, Birmingham, AL, USA

Vincent Sibaud, MD
Department of Oncodermatology, Institut Universitaire du Cancer – Toulouse Oncopole, Toulouse, France

Ximena Wortsman, MD
Institute for Diagnostic Imaging and Research of the Skin and Soft Tissues; Departments of Dermatology, University of Chile and Pontifical Catholic University of Chile, Santiago, Chile

Elvin G. Zook, MD (Deceased)
Formerly, Plastic Surgery Institute, Southern Illinois University, School of Medicine, Springfield, IL, USA
List of Abbreviations

3D three-dimensional
ACA anticardiolipin antibody
ACTH adrenocorticotropic hormone
ADFK acquired digital fibrokeratoma
ADL activities of daily living
AER apical ectodermal ridge
AIDS acquired immunodeficiency syndrome
ALHE angiolymphoid hyperplasia with eosinophilia
ALM acrolentiginous melanoma
AORN Association of Operating Room Nurses
APACHE acral pseudolymphomatous angikeraoma of children
APES aminopropyltriethoxysilane
AVA arteriovenous anastomoses
AVF arteriovenous fistula
BDD blistering distal dactylitis
BMP bone morphogenetic protein
BMZ basement membrane zone
BPNH bilateral periventricular nodular heterotopia
CA cyanoacrylate
CARI congenital autosomal recessive ichthyosis
CDC Centers for Disease Control
CEA carcinoembryonic antigen
CMC chronic mucocutaneous candidiasis
CMV cytomegalovirus
COIF congenital onychodysplasia of the index fingers
CT computed tomography
DBP dibutyl phthalate
DEB dystrophic epidermolysis bullosa
DIP distal interphalangeal
DLSO distal and lateral subungual onychomycosis
DMPS dimercapto-propane sulfonate
DMSA dimercaptosuccinic acid
DMSO dimethyl sulfoxide
EB epidermolysis bullosa
EBA epidermolysis bullosa acquisita
ED ectodermal dysplasia
EGFR epidermal growth factor receptor
EM electron microscopy
EMA epithelial membrane antigen
EO endonyx onychomycosis
FDA US Food and Drug Administration
FEF forced expiratory flow
FEV1 forced expiratory volume in 1 second
GVHD graft-versus-host disease
H&E hematoxylin and eosin
HEMA hydroxy-ethylmethacrylate
HFMD hand–foot–mouth disease
HIV human immunodeficiency virus
HOOD hereditary osteoonychodysplasia
HPV human papillomavirus
HSR high spatial resolution
HSV herpes simplex virus
HTLV human T-cell leukemia virus
IDS International Dermoscopy Society
ILM incident light microscopy
ILVEN inflammatory linear verrucous epidermal nevus
IP incontinentia pigmenti
IU international units
IVT ischemic venous thrombosis
KA keratoacanthoma
KID keratosis, ichthyosis, and deafness
LE lupus erythematosus
LED light-emitting diode
LM longitudinal melanonychia
MES multiple exostoses syndrome
MIC minimum inhibitory concentration
MIM Mendelian Inheritance in Man
MIP maximum intensity projection
MMA methylmethacrylate
MRI magnetic resonance imaging
MSH melanocyte-stimulating hormone
NAPSI Nail Psoriasis Severity Index
NTOM nerve territory-orientated macrodactyly
PA posteroanterior
PAI plasminogen activator inhibitor
PaO2 partial pressure of oxygen in arterial blood
PAS periodic acid–Schiff
PCB polychlorinated biphenyl
PCR polymerase chain reaction
PIU pterygium inversum unguis
PNF proximal nail fold
<table>
<thead>
<tr>
<th>Abbreviation</th>
<th>Full Form</th>
</tr>
</thead>
<tbody>
<tr>
<td>PRP</td>
<td>pityriasis rubra pilaris</td>
</tr>
<tr>
<td>PSO</td>
<td>proximal subungual onychomycosis</td>
</tr>
<tr>
<td>PUVA</td>
<td>psoralen ultraviolet A</td>
</tr>
<tr>
<td>PVC</td>
<td>polyvinyl chloride</td>
</tr>
<tr>
<td>PWSO</td>
<td>proximal white subungual onychomycosis</td>
</tr>
<tr>
<td>RA</td>
<td>rheumatoid arthritis</td>
</tr>
<tr>
<td>ROS</td>
<td>reactive oxygen species</td>
</tr>
<tr>
<td>RV</td>
<td>residual volume</td>
</tr>
<tr>
<td>SCC</td>
<td>squamous cell carcinoma</td>
</tr>
<tr>
<td>SE</td>
<td>spin echo</td>
</tr>
<tr>
<td>SLE</td>
<td>systemic lupus erythematosus</td>
</tr>
<tr>
<td>SLN</td>
<td>sentinel lymph node</td>
</tr>
<tr>
<td>SLR</td>
<td>single-lens reflex</td>
</tr>
<tr>
<td>SM</td>
<td>subungual melanoma</td>
</tr>
<tr>
<td>SNR</td>
<td>signal-to-noise ratio</td>
</tr>
<tr>
<td>SO</td>
<td>subungual onychomycosis</td>
</tr>
<tr>
<td>SSM</td>
<td>superficial spreading melanoma</td>
</tr>
<tr>
<td>STIR</td>
<td>short time inversion recovery</td>
</tr>
<tr>
<td>SWO</td>
<td>superficial white onychomycosis</td>
</tr>
<tr>
<td>T</td>
<td>tesla</td>
</tr>
<tr>
<td>TAR</td>
<td>thrombocytopenia absent radius</td>
</tr>
<tr>
<td>TDO</td>
<td>total dystrophic onychomycosis</td>
</tr>
<tr>
<td>TGF</td>
<td>transforming growth factor</td>
</tr>
<tr>
<td>TNF</td>
<td>tumor necrosis factor</td>
</tr>
<tr>
<td>TOWL</td>
<td>transonychial water loss</td>
</tr>
<tr>
<td>TTD</td>
<td>trichothiodystrophy</td>
</tr>
<tr>
<td>TUDDS</td>
<td>transungual drug delivery system</td>
</tr>
<tr>
<td>TUNEL</td>
<td>terminal deoxynucleotidyl transferase dUTP nick end labeling</td>
</tr>
<tr>
<td>US</td>
<td>ultrasonography</td>
</tr>
<tr>
<td>UV</td>
<td>ultraviolet</td>
</tr>
<tr>
<td>UVB</td>
<td>ultraviolet B</td>
</tr>
<tr>
<td>VEGF</td>
<td>vascular endothelial growth factor</td>
</tr>
</tbody>
</table>
Foreword

The fifth edition of Baran & Dawber’s Diseases of the Nails and their Management is a lovely tribute to this fascinating and distinctive keratinized structure. Based upon the cumulative and vast experience of the authors, the book offers insights that are both well honed and practical. There is also an appreciation of the spectrum of clinical presentations of the various dermatological disorders that can affect the nail unit. Although overlapping clinical and histopathological features can be seen when a specific disease involves the skin versus the nail unit, this textbook succeeds in emphasizing those findings that are unique to the latter. An abundance of high-quality clinical photographs, combined with beautiful dermoscopic images and exceptional schematics, provide the reader with a wealth of useful information. I was particularly struck by the sophisticated nature of the discussion on trauma-induced nail changes, a topic that is sometimes erroneously viewed as mundane but has to be accurately diagnosed on a daily basis.

Patients with nail disorders, as well as the clinicians who care for those patients, will clearly benefit from the knowledge contained in these chapters, from logical approaches to diagnosis to effective therapeutic interventions. I speak for my colleagues when I say we are lucky to have such a body of worthwhile information so nicely organized for our consumption.

Jean Bolognia, MD
Professor of Dermatology
Yale School of Medicine
Preface

Diseases of the nail unit have fascinated physicians for centuries, beginning with Hippocrates. The nail is considered to be the window to the body, manifesting signs of internal disease and clues to one's health. Over time, more and more nail signs of skin disease and tumors arising in the nail apparatus have been studied and revealed.

The first edition of Drs. Baran and Dawber's textbook *Diseases of the Nails and their Management*, published in 1984, was a pioneering work. It became a much needed reference for physicians and students wanting a compendium on nail disease. With each edition, the text has become more comprehensive, making it the most complete and most read textbook on the subject – the authority on nail disease.

With the fifth edition, we are pleased to have increased our group of editors to include more diverse, experienced nail clinicians from Belgium and Italy. Textbooks, like this one, require unwavering, dedicated work from our contributors as well as from our publisher. Carefully chosen nail clinicians have authored each chapter, each of them a recognized leader in their subspecialty of nail disease. We wish to thank our publisher, Wiley, for their support in our requests and our endeavor to ensure that the text remains the recognized leader in nail disease. We especially want to thank Dr. Robert Baran for his enthusiasm and dedication in ensuring that each of the five editions has been thoughtful and complete. He and his wife, Nicole – a dedicated, though behind-the-scenes, editor – make an unbeatable team.

The fifth edition of *Diseases of the Nails and their Management* has been expanded to include new diseases and updated treatments, improved chapter organization, and new online video supplements. It is our sincere hope that the fifth edition of *Diseases of the Nails and their Management* broadens your knowledge of nail disease and becomes your primary reference on this subject, as it has ours.

David de Berker
Mark Holzberg
Bianca Maria Piraccini
Bertrand Richert
Luc Thomas
About the Companion Website

This book is accompanied by a companion website:

www.wiley.com/go/BaranandDawber

The website includes:

- Videos of ultrasound imaging of the nail
- All images from the book
Part I

The Normal Nail and Nail Signs

Chapter 1

Science of the Nail Apparatus

David de Berker¹, Beth S. Ruben², and Robert Baran³

¹Bristol Dermatology Centre, Bristol Royal Infirmary, Bristol, UK
²Dermatology/Dermatopathology, University of California, San Francisco
Dermatopathology, Palo Alto Medical Foundation, Palo Alto, CA, USA
³Hon. Pr. of the University of Franche-Comté; Nail Disease Centre, Cannes, France

Gross anatomy and terminology

Knowledge of nail unit anatomy and terms is important for clinical and scientific work [1, 2]. The nail is an opalescent window through to the vascular nail bed. It is held in place by the nail folds, origin at the matrix, and attachment to the nail bed. It ends at a free edge distally, overlying the hyponychium. These structures are illustrated in Figs 1.1–1.4. Definitions of the components of the nail unit are as follows.

- **Nail plate (nail)**: durable keratinized structure which continues growing throughout life.
- **Lateral nail folds**: the cutaneous folded structures providing the lateral borders to the nail.
- **Proximal nail fold (posterior nail fold)**: cutaneous folded structure providing the visible proximal border of the nail, continuous with the cuticle. On the undersurface this becomes the dorsal matrix.
- **Cuticle (eponychium)**: the layer of epidermis extending from the proximal nail fold and adhering to the dorsal aspect of the nail plate.
- **Nail matrix (nail root)**: traditionally, this can be split into three parts [3]. The dorsal matrix is synonymous with the ventral aspect of the proximal nail fold. The intermediate matrix (germinative matrix) is the epithelial structure starting at the point where the dorsal matrix folds back on itself to underlie the proximal nail. The ventral matrix is synonymous with the nail bed and starts at the border of the lunula, where the intermediate matrix stops. It is limited distally by the hyponychium.
- **Lunula (half moon)**: the convex margin of the intermediate matrix seen through the nail. It is paler than the adjacent nail bed. It is most commonly visible on the thumbs and great toes. It may be concealed by the proximal nail fold.
- **Nail bed (ventral matrix, sterile matrix)**: the vascular bed upon which the nail rests, extending from the lunula to the hyponychium. This is the major territory seen through the nail plate.
- **Onychodermal band**: the distal margin of the nail bed has a contrasting hue in comparison with the rest of the nail bed [4]. Normally, this is a transverse...
band of 1–1.5 mm of a deeper pink (white) or brown (Afro-Caribbean). Its color, or presence, may vary with disease or compression, which influences the vascular supply (Fig. 1.5). Sonnex et al. [5] examined 1000 nails from thumbs and fingers in 100 subjects, alive and dead. In addition to clinical observation, they obtained histology from cadavers. Their findings are summarized in Table 1.1. The onychodermal band represents the first barrier to penetration of materials beyond the nail plate. Disruption of this barrier by disease or trauma precipitates a range of further events affecting the nail bed. The white appearance of the central band represents the transmission of light from the digit tip through the stratum corneum and up through the nail. If the digit is placed against a black surface, the band appears dark.

- **Hyponychium**: the cutaneous margin underlying free nail, bordered distally by the distal groove (Fig. 1.6).
- **Distal groove (limiting furrow)**: a cutaneous ridge demarcating the border between subungual structures and the digit pulp.
Embryology

Morphogenesis

8–12 weeks
Individual digits are discernible from the 8th week of gestation [3]. The first embryonic element of the nail unit is the nail anlage, present from 9 weeks as the epidermis overlying the dorsal tip of the digit. At 10 weeks, a distinct region can be seen and is described as the primary nail field. This almost overlies the tip of the terminal phalanx, with clear proximal and lateral grooves in addition to a well-defined distal groove. The prominence of this groove is partly due to the distal ridge, thrown up proximally, accentuating the contour. The primary nail field grows proximally by a wedge of germinative matrix cells extending back from the tip of the digit. These cells are proximal to both the distal groove and ridge. The spatial relationship of these two latter structures remains relatively constant as the former becomes the vestigial distal groove and the latter the hyponychium (Fig. 1.7).

13–14 weeks
Differential growth of the slowly developing primary nail field and surrounding tissue results in the emergence of overhanging proximal and lateral nail folds. Depending on the point of reference, the nail folds may be interpreted as overhanging [6] or the matrix as invaginating. By 13 weeks the nail field is well defined in the finger, with the matrix primordium underlying a proximal nail fold. By 14 weeks the nail plate is seen emerging from beneath the proximal nail fold, with elements arising from the lunula as well as more proximal matrix.

17 weeks to birth
At 17 weeks, the nail plate covers most of the nail bed and the distal ridge has flattened. From 20 weeks, the nail unit and finger grow in tandem, with the nail plate
abutting the distal ridge. This is now termed the hypo­nychium. The nail bed epithelium no longer produces kerato­hyalin, with a more parakeratotic appearance. By birth the nail plate extends to the distal groove, which becomes progressively less prominent. The nail may curve over the volar surface of the finger. It may also demonstrate koilonychia. This deformity is normal in the very young and a function of the thinness of the nail plate. It reverses with age.

Tissue differentiation

Keratins belong to the family of intermediate filament proteins. They are responsible for the tough resilient quality of nail. They are found within the cytoplasm. There are 54 human keratin genes with their keratins divided into three categories:

1) epithelial keratins/genes
2) hair keratins/genes
3) keratin pseudogenes.

Schweizer et al. [7] devised the reclassification of keratins according to the system described below to accommodate the changing knowledge of keratins in the context of the previous system (Table 1.2).

The element of common ground between hair and nail biology is reflected in many shared keratins that lend physical characteristics to the tissue. Hence, although nail biology is not acknowledged in this scheme, where there is a designation of hair keratin, it is common for it also to be a nail keratin and for the higher level of sulfur amino acids in the keratin to afford a larger number of intramolecular cross-links and greater physical stability and strength.

Keratin synthesis can be identified in the nail unit from the earliest stages of its differentiation [8]. In 12- and

Table 1.1 Clinical appearance of distal zones of the nail bed.

<table>
<thead>
<tr>
<th>Zone Subzone</th>
<th>Appearance</th>
</tr>
</thead>
<tbody>
<tr>
<td>Free edge</td>
<td>Clear gray</td>
</tr>
<tr>
<td>Onychocorneal band</td>
<td></td>
</tr>
<tr>
<td>I Distal pink zone</td>
<td>0.5–2 mm distal pink margin, may merge with free edge</td>
</tr>
<tr>
<td>II Central white band</td>
<td>0.1–1 mm distal white band representing the point of attachment of the stratum corneum arising from the digit pulp</td>
</tr>
<tr>
<td>III Proximal pink gradient</td>
<td>Merging with nail bed</td>
</tr>
</tbody>
</table>

Figure 1.5 (a) Onychodermal band. (b) Diagrammatic representation of the morphological features of the normal nail; detail of the distal physiological color bands are shown. Courtesy of T.S. Sonnex and W.A.D. Griffiths.

Figure 1.6 Distal nail unit in longitudinal excision. Onychodermal band (A) at the junction with the hyponychium (B) where a granular zone is again found along with acral compact stratum corneum.
13-week embryos, the nail–matrix anlage is a thin epithelial wedge penetrating from the dorsal epidermis into the dermis. This wedge is thought to represent the “ventral matrix primordium.” By week 15, hard keratins are seen throughout the nail bed and matrix. This could have significance concerning theories of nail embryogenesis and growth, where debate exists as to the contribution made by the nail bed to nail growth [3, 9–12]. However, at 22 weeks, the layer of hard keratin-positive cells remains very thin in the nail bed, whereas it is considerably thickened in the matrix. In the adult nail, there have been reports of both the presence [13] and absence [8, 14–16] of hard keratins in the nail bed.

Histological observation at 13 and 14 weeks reveals parakeratotic cells just distal to this nail plate primordium staining for sulphydryl groups. This contrasts to adjacent epithelium, suggesting the start of nail plate differentiation. This early differentiation represents matrix formation and Merkel cells have been detected in the matrix primordium of human fetuses between weeks 9 and 15 [17]. Merkel cells may play a role in the development of epidermal appendages and are detectable using monoclonal antibodies specific to keratin 20 (K20). Their role in ontogenesis would explain their disappearance from the nail matrix after week 22 [17]. However, this is not a universal finding, with an abundance of Merkel cells identified in the matrix of young adult and cadaver nail specimens in one study [18].

At the 13–22-week stage there is a coincident increase in the expression of hard keratins and the development of keratohyalin granules.

By 25 weeks, most features of nail unit differentiation are complete. Changes may still occur in the chemical constitution of the nail plate after this date. A decrease in sulfur and aluminum and a rise in chlorine have been noted as features of full-term newborns in comparison with the nail plate of premature babies [19]. An elevated aluminum level may correspond to bone abnormalities which lead to osteopenia.

Factors in embryogenesis

The nail plate grows from the 15th week of gestation until death. Many factors act upon it in this time and influence its appearance. Because it is a rugged structure, growing over a cycle of 4–18 months, it provides a record of the effects of these influences. To consider the different formative mechanisms, it is important to distinguish between:

- embryogenesis
- regrowth
- growth.

There is overlap between all these processes, with the main clues concerning embryogenesis deriving from fetal studies and analysis of congenital abnormalities.
Regrowth is the growth of the nail plate following its removal. This may be for therapeutic reasons or following accidental trauma with associated damage. Observation of this process adds to our understanding of both growth and embryogenesis. Growth is the continuous process of nail plate generation over a fully differentiated nail bed and hyponychium. Embryogenesis is the subject of this section.

In the chick limb bud formation, there is a complex interaction between mesoderm and ectoderm. Initially, the mesoderm induces the development of the apical ectodermal ridge (AER). The mesoderm then becomes dependent upon the AER for the creation of the limb. Removal of the AER results in a halt of mesodermal differentiation. Replacing the underlying mesoderm with mesoderm from another part of the limb primordium still results in normal differentiation [20]. However, the AER continues to be dependent upon the mesoderm, which must be of limb type. Replacement of limb mesoderm with somite mesoderm causes flattening of the AER. These morphogenetic interactions occur prior to cytodifferentiation [21]. In the human, cases of anonychia secondary to phenytoin [22] might implicate the drug at this stage, prior to 8 weeks. Drugs have been suggested as contributing to congenital nail dystrophies mainly affecting the index finger [23]. Attempts at characterizing a putative nail mesenchyme have involved ectopic nail studies in the newborn and mature nail unit. A CD10-positive population of dermal cells is located in the submatrix and nail bed dermis, which is common to the finding in mesenchyme of the hair follicle [24, 25]. In addition, one compartment has been reported as CD34 positive, which differentiates it from the nail bed where CD10 alone is found [26]. This zone of specialized submatrix tissue has been referred to as the onychodermis and can be identified in specialized magnetic resonance imaging [27].

Subsequent work on limb bud biology has explored the significance of the transcription factor LIMX1B in the mouse embryo limb formation. This factor is implicated in the dorsal/ventral polarity of the evolving limb and has been confirmed to have a similar role in humans. Loss of effective LIM1X function results in duplication of structures such that there might be a ventral ventral digit rather than dorsal ventral where the finger pulp is repeated on both sides of the digit [28]. The LIMX1B system also acts on genes determining development of the eye and urogenital tract, which is the basis for involvement of all these systems in nail–patella syndrome. In this pathology, the differentiation messages from the mesenchyme to the ectoderm appear to be communicated in a manner that might formally be described in observational limb bud experiments.

LIMX1B is thought to be mediated through the spondin pathway, where spondins are a family of proteins contributing to intracellular communication. In hereditary anonychia, there is a defect in R-spondin 4 secretion, where this protein would normally determine the activity of the Wnt/β catenin signaling system that is thought in turn to play a part in the initiation of nail unit formation [29–31]. Frizzled-6 is a Wnt receptor gene. In its absence a knockout mouse manifests a range of changes in the claw, including the downregulation of four hard nail keratins, K86, -81, -34, and -31, two epithelial keratins of significance in the nail unit, K6a and 6b, and transglutaminase-1. These changes are seen with an altered phenotype [32]. Similarly, where β catenin is deleted in knockout mice, nail formation and fingertip regeneration is completely lost, suggesting that the interruption of the Wnt signaling pathway has direct effects. Similar blockade of Wnt signaling results in extension of high Ki67 and K17 expression throughout the matrix, albeit without clear nail production [33]. R-spondin 2 is expressed in the AER in normal mouse limb development [34]. Mice bred to be deficient in this spondin have substantial congenital limb anomalies, with lack of phalangeal development and no nail unit [34]. Consistent with the model of mesenchyme inducing the overlying ectoderm, spondins have been identified in fibroblast cultures but not keratinocyte cultures [35].

Multiple other biological pathways appear relevant to the formation of a normal nail unit. Leucine-rich repeat-containing G protein-coupled receptor 5 and 6 (Lgr5 and -6) are part of the Wnt signaling pathway and associated with stem cell populations in different appendages. Lgr6 is found in the nail matrix and is thought necessary for nail unit regeneration following loss in mice [36]. The concept of a stem cell population is found in other appendages and in the nail it has been relatively difficult to establish such cell populations with confidence. Human embryos between 14 and 23 weeks assessed for expression of three candidate stem cell markers in the evolving nail unit demonstrate markers validated through their expression in the hair follicle bulge. These include PHLDA1 (Pleckstrin homology-like domain, family A, member 1), which is a protein-coding gene, and K15 and -19. These markers are not found in the matrix or nail bed, but have a transient expression in the proximal element of the ventral aspect of the proximal nail fold [37], where they are considered characteristic of stem cell differentiation [38]. A population of K15 label-retaining cells indicative of low turnover is found in a ring-like distribution around the nail root. They have potential to contribute to the nail plate or the nearby epidermis. Nail avulsion creates a wound environment that disposés them to the former, and this in turn appears influenced by bone morphogenetic factors [39]. Proximal matrix cells are characterized by expression of K17 in addition to the normal K14, while having a high proliferation rate as demonstrated through Ki67 and...
exhibiting a colony-forming ability in vitro; also features that fit with the role of stem cells [33].

Other small molecules with relevance include histone deacetylase and the transcription factor FOX1 (Forkhead box N1). Reduction of histone deacetylase 1 and 2 in the K14 promoter biopathways in mice leads to abnormal appendage formation in embryogenesis. This affects hair follicles and claw formation, with dystrophic hyperpigmented claws. This suggests a role for histone deacetylase in ectodermal differentiation and morphogenesis [40]. FOXN1 (Forkhead box N1) is a transcription factor of significance in thymus epithelium and T-cell differentiation. It is also found in the nail matrix. Mutations with significance to other embryological defects and altered hair are also seen with nail dystrophy. Typically this is koilonychia, which structurally usually corresponds to thinning of the nail [41].

Transgenic mice with changes to the Akt gene demonstrate absent nail and distal bone. Akt is a serine/threonine protein kinase implicated in cell signaling [42]. Although the spondins reside in the mesenchyme and appear relevant to the interaction between mesenchyme and ectoderm, Akt is epithelial and is thought to play a part in the action of bone morphogenetic protein (BMP). BMP is part of the transforming growth factor (TGF)-β family of mediators. It is found in many different forms with a range of morphogenetic roles. In relation to the formation of the nail unit, it has been proposed that there is a two-way process whereby it is supportive of nail unit development, but equally that the nail unit plays a part in the regeneration of the distal phalanx when it is lost through trauma in infancy [43]; these processes may in part be mediated through BMP4.

Congenital abnormalities provide clinical examples of instances where the role of a BMP or similar factor appears central. Congenital onychodysplasia of the index fingers (COIF) is frequently associated with abnormalities of the terminal phalanges and interphalangeal joints [44]. The nail may be absent, small, or composed of several small nails on the dorsal tip of the affected finger. The bony abnormality varies, with the most marked change being bifurcation of the terminal phalanx on lateral radiographs [45]. However, a bony abnormality is not mandatory in this condition or other conditions with ectopic nail [46]. A normal nail may overlie an abnormal bone on other than the index finger [47]. COIF appears to demonstrate an association between abnormalities of bone and nail, rather than the presence of a strict relationship. It may represent a fault of mesoderm/ectoderm interaction at the stage when these layers are mutually dependent. It has been suggested that a vascular abnormality may provide the common factor between pathology in the two embryonic layers [47]. This would also be consistent with the part played by BMP in vascular development in embryogenesis [48]. If this is the case, it appears likely that any vascular abnormality arises due to a defect of patterned embryogenesis rather than a random event, given that a form of COIF can occur in the great toe of individuals with involved fingers [49].

An interpretation based upon a mutual mesodermal and ectodermal fault would fit with the observation of two cases of congenital anonychia and hypoplastic nails combined with hypoplastic phalanges [50] or brachydactyly [51, 52]. These cases were used as a foil for the suggestion of a mechanism of “bone-dependent nail formation.” It might also be argued in reverse that the bone was dependent upon the nail.

Histological preparation

When submitting a nail unit specimen for histology, it is important to have some communication with the pathologist to whom you are submitting it, and for he/she in turn to guide the laboratory staff with respect to processing it. Such specimens can be difficult on multiple levels to optimally handle, and many pathologists lack familiarity with this category of specimen. It is helpful to orient it, depending on the type of specimen submitted [51]. For example, in a longitudinal excision, there is inherent orientation when the specimen is maintained in its natural longitudinal axis, and, in fact, the laboratory should be instructed to maintain this upon processing, without sectioning it in the usual transverse style (i.e. avoid “breadloafing”) (Fig. 1.8). In a lateral longitudinal biopsy, one might however wish to indicate to the laboratory to embed on the edge away from the nail fold, as it might contain more helpful information. For more irregular shave and punch specimens and excisions, placing the delicate specimen on a piece of paper or nail template and inking on the paper provides helpful information. For more irregular shave and punch specimens and excisions, placing the delicate specimen on a piece of paper or nail template and inking on the paper near the distal end may also allow it to be sectioned, while maintaining some orientation and allowing the technician to know which surface is “up” (Fig. 1.8b). This also provides a mechanism to prevent thinner specimens from curling. Specimens containing nail plate and another containing soft tissue, for example a shave or punch, should be submitted in separate specimen bottles to facilitate processing, embedding, and cutting.

High-quality sections of the nail unit can be difficult to obtain. The nail plate is very hard and tends to shatter and fold in the course of routine histological processing. In biopsies containing nail plate and soft subungual and periungual tissue, the nail plate can be torn from the matrix and other adjacent structures by the microtome. Laboratories unused to nail histology will often have difficulty, may contact the clinician for advice, be slow to provide a result, and produce sections of suboptimal quality. Such problems can be diminished using a range of techniques to soften the nail plate. Some of them may be less practical and too harsh if there are soft tissue attachments requiring histological examination.
Nail softening techniques

Nail alone

There are a variety of different techniques to soften the nail plate. Some of them are not practical in the modern laboratory where speedy results are expected and the time available for technicians to spend on extra measures may be limited, but they will be discussed for historical perspective. Lewis [3] recommended routine fixation in 10% formalin and processing as usual. That is how most laboratories handle such specimens. Earlier methods employed fixation with potassium bichromate, sodium sulfate, or sodium bisulfite and water. The section is then decalcified with nitric acid and embedded in collodion. Alkiewicz and Pfister [53] recommended softening the nail with thioglycolate or hydrogen peroxide. Nail fragments are kept in 10% potassium thioglycolate at 37°C for 5 days or in 20–30% hydrogen peroxide for 5–6 days. The nail is then fixed by boiling in formalin for 1 min before cutting 10–15 mm sections.

Although softening of nail clippings for histology is not mandatory, it is possible and may be helpful. Suarez et al. [54] suggest soaking the clipping for 2 days in a mix of mercuric chloride, chromic acid, nitric acid, and 95% alcohol. The specimen is then transferred to absolute alcohol, xylene, and successive paraffin mixtures, sectioned at 4 mm, and placed on gelatinized slides. An alternative method, described for preserving histological detail in the nail plate, entails fixation in a mix of 5% trichloroacetic acid and 10% formalin for the initial 24 h [55]. This is followed by a modified polyethylene glycol–pyroxylin embedding method. Ultrathin sections can be provided by embedding the nail in plastic such as 2-hydroxyethyl methacrylate [56].

In current clinical practice, one can use simpler and quicker methods with products containing combinations and dilutions of sodium hydroxide (NaOH), calcium hydroxide (CaOH), and thioglycolate [57–59]. Fabric softener, Mollifex Gurr (ethanol, methanol, acetone, glycerin, 4-hexylresorcinol; VWR International Ltd), and hand/dishwashing soap have all been utilized. A commercial nail-softening agent containing 17% potassium hydroxide (Fig. 1.9), Nail Prep (Stat Lab Medical Products, McKinney, TX, USA), can be used after nail processing, soaking for 15 min. It can also be used in between taking sections by application with a cotton swab. The author’s histology team has also used this after an initial 4–6 h in 10% household ammonia prior to processing with excellent results. An over-the-counter depilatory agent, Nair (Church and Dwight, Ewing, NJ, USA) [60], containing CaOH, NaOH, and thioglycolate, can be diluted 2:1 with water and used to soak the nail for 2–3 h, and then it is processed as usual after rinsing. Many pathologists who work with nail specimens have their own approaches to handling such specimens depending also on local availability of reagents such as these [61]. Another simple method involves simply soaking the completed paraffin block in water, such as in a water bath in the histology laboratory, for 15 min before cutting to soften the nail plate.

Nail and soft tissue

In nail biopsies containing epithelium and/or soft tissue, more gentle methods of preparation are necessary, but the 17% potassium hydroxide and depilatory agents methods described above are also acceptable. The specimen can also be soaked in distilled water for a few hours

Figure 1.8 Use of nail template for nail biopsy specimen submission. (a) Before biopsy. (b) Longitudinal excision for diagnosis of nail dystrophy. (c) Specimen placed on a nail template prior to submission in formalin to maintain orientation. Courtesy of Monica Lawry.
before placing in formalin [62]. Twelve hours in 10% formalin followed by 3 days in 3% phenol prior to embedding is reported to achieve good results [63]. After routine fixation and embedding, permanent wave solution (of the type used in hairdressing), thioglycolate, or 10% potassium hydroxide solution can be applied with a cotton swab to the surface of the paraffin block every two or three sections, similar to the methods above for nail plate. Lewin et al. [57] suggested applying 1% aqueous polysorbate 40 to the cut surface of the block for 1 h at 4°C. Preparations containing acids, such as nitric acid used in decalcification solutions, should not be used on epithelium or soft tissue. They may interfere with other testing that one may want on such specimens, including some immunostains depending on intact DNA, such as proliferation markers, and molecular analysis [64, 65].

Sections will sometimes adhere to normal slides, but when there is nail alone the material tends to curl as it dries and may fall off. This means that it may be necessary to use gelatinized or 3-aminopropyltriethoxysilane (APES) slides. Albumin can also be used before placing the sections on the slide to improve adherence. Attention should be paid to avoiding folding of sections. Given the difficulty of obtaining high-quality sections, it may be necessary to cut at additional levels to maximize the chance of obtaining suitable sections.

Routine staining with hematoxylin and eosin is sufficient for most cases. Periodic acid–Schiff (PAS) and Grocott’s silver stain can be used to demonstrate fungi; a blancophore fluorochromation selectively delineates fungal walls [66]. More recently, Gomori methenamine silver (GMS) stain has been advocated following pretreatment with chromic acid and sodium bisulfite [67]. There has been some recent discussion as to whether PAS or GMS staining is superior for identification of fungi in the nail, but they are probably equivalent, and PAS is much less labor intensive and less expensive to perform [68, 69]. Some of the more representative material in a nail sample for histology for fungus may be in the crumbling substance on the ventral aspect. This can be examined separately but requires a container such as a paper lens container to prevent dispersal of the material and to avoid problems with preparing sections [56]. Toluylene blue at pH 5 allows better visualization of the details of the nail plate [62, 63]. Fontana–Masson stain demonstrates melanin. Hemoglobin is identified using a modified diaminobenzidine reaction [70]. Prussian blue and Perl stains are not helpful in the identification of blood in the nail as they are specific to the hemosiderin product of hemoglobin breakdown caused by macrophages, which does not occur in the nail [53, 64, 65].

Masson–Goldner’s trichrome stain is very useful to study the keratinization process, and Giemsa stain reveals slight changes in the nail keratin. These are not used widely in routine clinical practice.

Standard techniques for microwave antigen retrieval for immunohistochemistry, routine polymerase chain reaction studies, and terminal deoxynucleotidyl transferase dUTP nick end labeling (TUNEL) assays all appear feasible in combined soft tissue and nail specimens. Molecular analysis is also possible [71].

Polarization microscopy shows the regular arrangement of keratin filaments, and birefringence is said to be absent in disorders of nail filaments, and birefringence is said to be absent in disorders of nail formation such as leukonychia.

**Routine histology**

A longitudinal biopsy of the nail unit will yield a specimen with sampling of all the main histological zones of the appendage (Fig. 1.10). The cells of the nail matrix are distinct from the adjacent nail bed distally and the ventral...
surface of the nail fold, lying at an angle above. The nail matrix is the thickest area of stratified squamous epithelium in the midline of the nail unit, comparable with the hyponychium. There are longitudinally oriented epithelial ridges (unlike rete ridges) characteristically descending at a slightly oblique angle, their tips pointing distally. Laterally, the matrix ridges are less marked, whereas those of the nail bed and nail folds become prominent.

Unlike the overlying nail fold, but like the nail bed, the matrix has no granular layer (Fig. 1.11). The demarcation between overlying nail fold and matrix is enhanced by the altered morphology of the epithelial ridges. At their junction at the apex of the matrix and origin of the nail, the first matrix epithelial ridge may have a bobbed appearance like a lopped sheep’s tail. PAS staining is marked at both the distal and proximal margins of the intermediate matrix (Fig. 1.12). Distally, there is often a step reduction in the epithelial thickness at the transition of the matrix with the nail bed. This represents the edge of the lunula.

Nail is formed from the matrix as cells become larger and paler and eventually the nucleus disintegrates. There is progression with flattening, elongation, and further pallor. Occasionally, retained shrunken or fragmented nuclei persist to be included into the nail plate. Lewis [3] called these “pertinax bodies.” They can give an impression of the longitudinal progression of growth in the nail plate (Fig. 1.13).

Melanocytes are present in the matrix where they reach a density of up to 300/mm² [71–75]. This can also be expressed as the number of melanocytes per linear millimeter of matrix epidermis examined (Fig. 1.14). Figures for this are a mean of 7.5, median of 7.7, and range of 4–9 [76] (Table 1.3).
Dendritic cells are found in the epibasal layers and are most prominent in the distal matrix [73–75]. This point can be refined in terms of the functional status of the melanocytes. Cameli et al. [19] described melanocytes of the proximal matrix as being in a single compartment of largely dormant cells. Those in the distal matrix are in two compartments, with both a dormant and functionally differentiated population. Longitudinal melanonychia most commonly arises from pigment contributed to the nail plate by these differentiated distal melanocytes. Cameli et al. also defined a smaller population of nail bed melanocytes, with approximately 25% of the number found in the matrix, and none of these were differentiated in terms of 3,4-dihydroxy-l-phenylalanine (DOPA) staining. This differs from the observations of de Berker et al. [74], who noted that the nail bed lacked melanocyte markers.

The suprabasal location of nail matrix melanocytes can lead to difficulties in the interpretation of histological specimens obtained to exclude atypicality in instances of melanonychia, given that suprabasal scatter of melanocytes is a sign of atypia in normal epidermis. HMB-45, Melan-A, MiTF, and SOX-10 are useful markers of nail matrix melanocytes. S100, while helpful in desmoplastic melanoma at this and other sites with

<table>
<thead>
<tr>
<th>Pathology</th>
<th>Mean</th>
<th>Median</th>
<th>Range</th>
</tr>
</thead>
<tbody>
<tr>
<td>Invasive melanoma</td>
<td>102</td>
<td>92.5</td>
<td>52–212</td>
</tr>
<tr>
<td>In situ melanoma</td>
<td>58.9</td>
<td>51</td>
<td>39–136</td>
</tr>
<tr>
<td>Lentigo</td>
<td>15.3</td>
<td>14</td>
<td>5–31</td>
</tr>
<tr>
<td>Normal control</td>
<td>7.7</td>
<td>7.5</td>
<td>4–9</td>
</tr>
</tbody>
</table>

Reproduced from Amin [76] with permission from Lippincott, Williams and Wilkins.
respect to staining dermal melanocytes, is variable in its ability to stain matrix melanocytes. In spite of these difficulties in interpretation, melanoma is a relatively rare cause of nail unit pigmentation, although it may be necessary to exclude it histologically, particularly in white adults [73, 77, 78].

Melanin in the nail plate is composed of granules derived from matrix melanocytes [9]. Longitudinal melanonychia may be a benign phenomenon, particularly in Afro-Caribbean people: 77% of black people will have a melanonychia by the age of 20 and almost 100% by age 50 [79, 80]. The Japanese also have a high prevalence of longitudinal melanonychia, being present in 10–20% of adults [81]. In a study of 15 benign melanonychia cases in Japanese patients, they were found to arise from an increase in activity and number of DOPA-positive melanocytes in the matrix, not a melanocytic nevus [72]. A survey of fingers and toes of 2457 Chinese patients found none with melanonychia below the age of 20; 0.6% in those between 20 and 29; and 1.7% in those over 50 [82]. A French study of white patients found a 1.4% prevalence in the community and 12.6% prevalence in hospitalized patients [83]. The difference may have in part reflected different clinical sensitivity among community and hospital clinicians. In all studies, where mentioned, the thumb and great toe are the most commonly affected digit. Longitudinal melanonychia in white patients is more sinister; Oropeza [84] stated that a subungual pigmented lesion in this group has a higher chance of being malignant than benign.

There is only a thin layer of dermis dividing the matrix from the terminal phalanx. This has a rich vascular supply (see “Vascular supply”) and an elastin and collagen infrastructure giving attachment to periosteum.

**Electron microscopy**

Transmission electron microscopy confirms that, in many respects, matrix epithelium is similar to normal cutaneous epithelium [85–91]. The basal cells contain desmosomes and hemidesmosomes and interdigitate freely. Differentiating cells are rich in ribosomes and polysomes and contain more RNA than equivalent cutaneous epidermal cells. As cell differentiation proceeds towards the nail plate, there is an accumulation of cytoplasmic microfibrils (7.5–10 nm). These fibrils are haphazardly arranged within the cells up to the transitional zone. Beyond this, they become aligned with the axis of nail plate growth.

Membrane-coating granules (Odland bodies) are formed within the differentiating cells. They are discharged onto the cell surface in the transitional zone and have been thought to contribute to the thickness of the plasma membrane. They may also have a role in the firm adherence of the squamous cells within the nail plate, which is a notable characteristic [91]. The glycoprotein characteristics of cell membrane complexes isolated from nail plate may reflect the constituents of these granules [92].

Mitochondria are degraded during the transitional phase, while RNA-containing ribosomes are evident up to the stage of plasma membrane thickening. Vacuoles containing lipid and other products of cytolysis are seen at the transitional stage. Dorsal matrix cells start to show nuclear shrinkage at this point, whereas the nuclei in the matrix remain intact to a higher level.

Electron microscopy has been used to examine the nail plate in detail in fungal disease [93], alopecia areata [94], connective tissue diseases [95], and psoriasis [96].

**Regional anatomy**

**Nail matrix and lunula**

For simplicity, the nail matrix (syn. intermediate matrix) will be defined as the most proximal region of the nail bed extending to the lunula. This is commonly considered to be the source of the bulk of the nail plate, although further contributions may come from other parts of the nail unit (such as the nail bed). Contrast with these other regions helps to characterize the matrix.

The matrix is vulnerable to surgical and accidental trauma; a longitudinal biopsy of greater than 3 mm width is likely to leave a permanent dystrophy [97] (Fig. 1.10). Once matrix damage has occurred, it is difficult to effectively repair it [98–100]. This accounts for the relatively small amount of histological information on normal nail matrix.

It is possible to make distinctions between distal and proximal matrix on functional grounds, given that 81% of cell numbers in the nail plate are provided by the proximal 50% of the nail matrix [101] and surgery to distal matrix is less likely to cause scarring than more proximal surgery. Clinically, the matrix is synonymous with the lunula, or half moon, which can be seen through the nail emerging from beneath the proximal nail fold as a pale convex structure. This is most prominent on the thumb, becoming less prominent in a gradient towards the little finger. It is rarely seen on the toes. The absence of a clinically identifiable lunula may mean that the vascular tone of the nail bed and matrix has obscured it or that the proximal nail fold extends so far along the nail plate that it lies over the entire matrix.

High-resolution magnetic resonance imaging identifies the matrix and dermal zones beneath [102, 103]. Drapé et al. [103] described a zone beneath the distal matrix where there is loose connective tissue and a dense microvascular network. It may be the presence of this network that accounts for the variable sign of red lunulae in some systemic conditions [104, 105]. However, the histological observations of Lewin [106] suggested that there is diminished vascularity and increased dermal
collagen beneath the matrix contributing to the pallor, which helps identify the area. This has been confirmed in a more recent study utilizing injection of gelatinized Indian ink into amputation specimens [107]. The close association between the nail matrix and joint apparatus results in magnetic resonance imaging changes in the tendon sheath and matrix coincidentally [108] and may demonstrate changes in the matrix prior to the onset of any clinical nail disease [109].

The thinner epidermis of the nail bed may account for the contrast between the white and pink appearance of the lunula and bed, respectively [110]. Many suggestions have been made to account for the appearance of the lunula [75, 85, 106, 111] (Box 1.1).

Macroscopically, the distal margin of the matrix is convex and is easily distinguished from the contiguous nail bed once the nail is removed, even if the difference is not clear prior to avulsion. The nail bed is a more deep red and has surface corrugations absent from the matrix. At the proximal margin of the matrix, the contour of the lunula is repeated. At the lateral apices, a subtle ligamentous attachment has been described, arising as a dorsal expansion of the lateral ligament of the distal interphalangeal joint [112]. Lack of balance between the symmetrical tension on these attachments may explain some forms of acquired and congenital malalignment [113].

Nail bed and hyponychium

The nail bed extends from the distal margin of the lunula to the hyponychium. It is also called the ventral matrix, depending on whether or not you believe that it contributes to the substance of the nail plate (see “Nail growth”). Avulsion of the nail plate reveals a pattern of longitudinal epidermal ridges stretching to the lunula (Fig. 1.15). On the underside of the nail plate is a complementary set of ridges, which has led to the description of the nail being led up the nail bed as if on rails (Fig. 1.16). The small vessels

<table>
<thead>
<tr>
<th>Box 1.1 Possible causes for the pale appearance of the lunula</th>
</tr>
</thead>
<tbody>
<tr>
<td>● The surface of the nail is smoother and more shiny proximally.</td>
</tr>
<tr>
<td>● The thicker epidermis of the lunula obscures the underlying vasculature.</td>
</tr>
<tr>
<td>● The nail attachment at the lunula is less firm, allowing greater refraction and reflection at the nail–soft tissue interface.</td>
</tr>
<tr>
<td>● The underlying dermis has fewer capillaries in it.</td>
</tr>
<tr>
<td>● The underlying dermis is of looser texture.</td>
</tr>
<tr>
<td>● The matrix epithelium in the lunula has more nuclei than the nail bed, making it appear parakeratotic with an altered color.</td>
</tr>
</tbody>
</table>

Figure 1.15 The epidermis of the nail bed has longitudinal ridges visible after nail avulsion.

Figure 1.16 The undersurface of the nail plate shows longitudinal ridging that matches that seen on the nail bed. This pattern is lost at the margin of the lunula, where the nail is in continuity with the matrix from which it arises.
of the nail bed are orientated in the same axis. This can be demonstrated by using corrosion casting from cadaver digits [114] and is clinically manifested by splinter hemorrhages (Figs 1.17, 1.18), where heme is deposited on the undersurface of the nail plate and grows out with it. The free edge of a nail loses the ridges, suggesting that they are softer than the main nail plate structure. The nail bed also loses these ridges shortly after loss of the overlying nail. It is likely that the ridges are generated at the margin of the lunula on the ventral surface of the nail to be imprinted upon the nail bed.

The epidermis of the nail bed is thin over the bulk of its territory. It becomes thicker at the nail folds, where it develops rete ridges. It has no granular layer except in disease states. The dermis is sparse, with little fat, has firm collagenous adherence to the underlying periosteum, and has no sebaceous or follicular appendages. Sweat ducts can be seen at the distal margin of the nail bed using in vivo magnification (Fig. 1.19) [111].

The hyponychium lies between the distal ridge and the nail plate and represents a space as much as a surface. Perrin [115] has described an analog of the hair follicle isthmus at the junction of the hyponychium and nail bed, referred to as the nail isthmus, leading on to the nail infundibulum, which he proposed would replace the term hyponychium. The distal ridge (see “Factors in embryogenesis”) is seen from the 10th week of gestation onwards. The hyponychium and onychocorneal band may be the focus or origin of subungual hyperkeratosis in some diseases such as pityriasis rubra pilaris (see Table 1.8) or pachyonychia congenita.

The hyponychium can be extended into a pathological structure vulnerable to bleeding and pain with minimal trauma or nail clipping known as pterygium inversum unguis [116]. There is tough, fibrotic tissue tethering the free edge of the nail plate to the underlying soft structures. It is found in both congenital [117] and acquired forms [118]. The proposed etiology and patterns are various. Patterson [118] proposed that it was a combination of a genetic predisposition and microvascular ischemia.

The hyponychium and overhanging free nail provide a crevice which is a reservoir for microbes, relevant in surgery and the dissemination of infection. After 10 min of scrubbing the fingers with povidone-iodine, nail clippings were cultured for bacteria, yeasts, and molds [119]. In 19 out of 20 patients, *Staphylococcus epidermidis* was isolated, seven patients had an additional bacterium, eight had molds, and three had yeasts. These findings could have significance for both surgeons and patients. However, in a randomized trial of chlorhexidine scrub used with or without a nail brush, the nail brush did statistically diminish the number of colony-forming units obtained from the scrubbed hand [120].
The hand-to-mouth transfer of bacteria is suggested by the high incidence of *Helicobacter pylori* beneath the nails of those who are seropositive for antibodies and have oral carriage. Dowsett et al. [121] found that 58% of those with tongue *H. pylori* had it beneath the index fingernail, representing a significant (*p = 0.002*) association.

**Nail folds**

The proximal and lateral nail folds give purchase to the nail plate by enclosing more than 75% of its periphery. They also provide a physical seal against the penetration of materials to vulnerable subungual and proximal regions.

The epidermal structure of the lateral nail folds is unremarkable, and comparable with normal skin. There is a tendency to hyperkeratosis, sometimes associated with trauma. When the trauma arises from the ingrowth of the nail, considerable soft tissue hypertrophy can result, with repeated infection (such as ingrowing nails).

The proximal nail fold has three parts. Its upper aspect is normal glabrous skin, providing no direct influence upon the nail plate. At the point where its distal margin meets the nail plate, it forms the cuticle (eponychium). In health, the cuticle adheres firmly to the dorsal aspect of the nail plate, achieving a seal. Its disruption may be associated with systemic disorders (collagen vascular disease) or local dermatoses. In the latter, it may be the avenue for contact allergens or microbes. The ventral aspect of the proximal nail fold is apposed to the dorsal aspect of the nail. It contrasts with the adjacent matrix by being thinner, with shorter rete ridges, and having a granular layer. Keratins expressed in the proximal nail fold may differ on its dorsal and ventral aspects and can contrast with expression elsewhere in the nail unit [14] (see “Nail growth”).

The proximal nail fold has significance in four main areas.

1) It may contribute to the generation of the nail plate through a putative dorsal matrix on its ventral aspect.
2) It may influence the direction of growth of the nail plate by directing it obliquely over the nail bed.
3) Nail fold microvasculature can provide useful information in some pathological conditions.
4) When inflamed, it can influence nail plate morphology as seen in eczema, psoriasis, habit–tic deformity, and paronychia.

The first two issues are dealt with in the section on nail growth (see “Nail growth”); the last two under vasculature (see “Vascular supply”) and Chapter 14.

**Immunohistochemistry of periungual tissues**

**Keratins**

The most extensive immunohistological investigations of the nail unit have utilized keratin antibodies. The nail plate [13, 93], human embryonic nail unit [7, 13, 122], accessory digit nail unit [123, 124], adult nail unit [14, 46, 122, 125], and mouse claws [126] have all been examined (Table 1.4).

Using monospecific antibodies, de Berker et al. [15, 123] detected K1 and K10 in a suprabasal location in the matrix and noted their absence from the nail bed (Fig. 1.20) (see “Nail growth” and “Nail plate”). K1 and K10 are “soft” epithelial keratins found suprabasally in normal skin [127] and are characteristic of cornification with terminal keratinocyte differentiation. Their absence from normal nail bed is reversed in disease where nail bed cornification is often seen, alongside development of a granular layer and expression of K1 and K10 [128]. The development of a granular layer in nail matrix and bed epithelium can be interpreted as a pathological sign in nail histology, seen in a range of diseases and probably associated with changes in keratin expression [129].

Ha-1 (K31), a “hard” keratin, is found in the matrix. K7 has been found at other sites in the nail unit and hair follicle, whereas Ha-1, detected by the monoclonal antikeratin antibody LH TRIC 1, is limited to the matrix of the nail (Fig. 1.21) and the germinal matrix of the hair follicle [16, 123]. Other hard hair/nail keratins have been highlighted as limited to the matrix where K85 (hHb5), K34 (hHa4), K81 (hHB1), and K86 (hHB6) have all been found within the conventional boundaries of the matrix. K19 is probably not found in the adult matrix [8, 15, 66].

<table>
<thead>
<tr>
<th>Table 1.4 Keratins in the nail unit.</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Type II keratins</strong></td>
</tr>
<tr>
<td>K1</td>
</tr>
<tr>
<td>K5</td>
</tr>
<tr>
<td>K6a</td>
</tr>
<tr>
<td>K6b</td>
</tr>
<tr>
<td>K17</td>
</tr>
<tr>
<td>K81 (Hb1)</td>
</tr>
<tr>
<td>K85 (Hb5)</td>
</tr>
<tr>
<td>K86 (Hb6)</td>
</tr>
<tr>
<td>K38 (Ha8)</td>
</tr>
</tbody>
</table>

**Keratins expressed transiently in embryogenesis**

<table>
<thead>
<tr>
<th>Keratins</th>
<th>Mice develop pachyonychia-like disease when they have mutations for this keratin. Also associated with tooth decay</th>
</tr>
</thead>
<tbody>
<tr>
<td>K19</td>
<td></td>
</tr>
<tr>
<td>K15</td>
<td>+</td>
</tr>
</tbody>
</table>

**Keratins known to have relevance to the nail unit through human or rodent disease genomics**

- **K75**
  - Mice develop pachyonychia-like disease when they have mutations for this keratin. Also associated with tooth decay

- **K74**
  - Ectodermal dysplasia with woolly hair and nail defects
However, Moll et al. [8] did detect K19 at this site in 15-week embryo nail units. K19 is also found in the outer root sheath of the hair follicle and lingual papilla [14].

More recently, K6, -15, -16, -17, -18, and -19 have all been found at different subungual locations and phases in nail matrix development with a variety of attributed functions. K6, -16, and -17 have been implicated in innate immunity with the ability to trigger immunological responses [130]. K6 found beneath the normal nail is known to be necessary for the release of antibacterial peptides in response to *Pseudomonas aeruginosa*, a bacterium common in the subungual space of an onycholytic nail [131]. Human papillomavirus 16 is implicated in the development of subungual squamous cell carcinoma as well as carcinoma of the cervix. It complexes with K18 to result in its degradation, and this in turn may contribute to its pathogenicity as a carcinogen [132].

The colocalization of hard and soft keratins within single cells of the matrix has been observed by several workers in bovine hoof [133] and human nail [15, 134, 135], suggesting that these cells are contributing both forms of keratin to the nail plate. This dual differentiation continues into in vitro culture of bovine hoof matrix cells [134]. Culture of human nail matrix confirms the persistence of hard keratin expression [135, 136].

Markers for K8 and K20 are thought to be specific to Merkel cells in the epidermis. Positive immunostaining for these keratins has been noted by Lacour et al. [137] in adult nail matrix and de Berker et al. [16] in infant accessory digits. Some workers have failed to detect Merkel cells and, while it seems likely that they are present in fetal and young adult matrix, it may be that the cells are less common or absent as people age [138].
Nail bed expression of K6a, -6b, -16, and -17 has significance, with the characterization of the underlying fault in some variants of pachyonychia congenita where abnormalities of nail bed keratin lead to a grossly thickened nail plate. Mutations in the gene for K17 have been reported in a large Scottish kindred with the PC-2, or Jackson–Lawler, phenotype [139, 140]. There is a cross-over with steatocystoma multiplex, where the same mutation of K17 may cause this phenotype, which appears to be independent of the specific K17 mutation [141–143]. Mutations in the gene coding for K6b produce a phenotype seen with K17 gene mutations [144]. Mutations in the K6a [145] and K16 [140] genes have been reported in PC-1, originally described as the Jadassohn–Lewandowsky variant of pachyonychia congenita.

Expression of K6, -16, and -17 extends beyond the nail bed onto the digit pulp and is thought to match the physical characteristics of this skin, which is adapted to high degrees of physical stress [146]. In particular, expression of K17 is found at the base of epidermal ridges, which might also support the idea that this keratin is associated with stem cell function.

It is important to recognize that the hard keratins responsible for the characteristics of nail tissue are the product of an interaction between underlying mesenchyme fibroblasts and the overlying epithelium. Hard nail keratins can be induced both in vivo and in vitro using nail matrix mesenchyme and non-nail epithelium [147, 148]. Induced expression of hard keratin is not the same as producing a nail, as the product of these experiments can be a poorly organized structure only recognizable as nail in immunohistochemical terms [149]. The specific nature of the nail mesenchyme may correspond to the presence of nail mesenchyme versican, where versican is a chondroitin sulfate proteoglycan and a member of the lecticans family [150].

**Non-keratin immunohistochemistry**

Involucrin is a protein necessary for the formation of the cellular envelope in keratinizing epithelia. It is strongly positive in the upper two-thirds of the matrix and elsewhere in the nail unit [151] and weakly detected in the suprabasal layers. Panecrumblin and scellin are also detected in the matrix [151]. The antibody HHF35 is considered specific to actin. It has been found to show a strong membranous staining and weak cytoplasmic staining of matrix cells.

In the dermis, vimentin was strongly positive in fibroblasts and vascular endothelial cells. Vimentin and desmin were expressed in the smooth muscle wall of some vessels. S100 stain, for cells of neural crest origin, revealed perivascular nerves, glomus bodies, and Meissner’s corpuscles distally.

Filaggrin could not be demonstrated in the matrix by electron microscopy [14]. However, Manabe and O’Guin [152] have detected the coexistence of trichohyalin and filaggrin in monkey nail, located in the area they term the “dorsal matrix,” which is likely to correspond to the most proximal aspect of the human nail matrix as it merges with the undersurface of the proximal nail fold. Kitahara and Ogawa [135] have identified filaggrin in the human nail in the same location, and Mlitz [153] and O’Keefe et al. [154] have found trichohyalin in the “ventral matrix” of human nail, which is synonymous with the nail bed. Manabe and O’Guin [152] noted that these two proteins coexist with K6 and K16, which are more characteristic of nail bed than matrix. It is argued that filaggrin and trichohyalin may stabilize the intermediate filament network of K6 and K16, which are normally associated with unstable or hyperproliferative states. When pathological mutations of the filaggrin gene and those for K16 coexist, the phenotype may be more severe than in the parent with the original isolated keratin gene mutation [155].

The plasminogen activator inhibitor type 2 has been detected in the nail bed and matrix, where, it has been argued, it may have a role in protecting against programmed cell death [156]. The basement membrane zone of the entire nail unit has been examined, employing a wide range of monoclonal and polyclonal antibodies [124]. Collagen VII, fibronectin, chondroitin sulfate, and tenascin were among the antigens detected. All except tenascin were present in a quantity and pattern indistinguishable from normal skin. Tenascin was absent from the nail bed, which was attributed to the fact that the dermal papillae are altered or considered absent (Table 1.5).

**Nail plate**

The nail plate is composed of compacted keratinized epithelial cells. It covers the nail bed and intermediate matrix and is curved in both the longitudinal and transverse axes. This allows it to be embedded in nail folds at its proximal and lateral margins, which provide strong attachment and make the free edge a useful tool. This feature is more marked in the toes than in the fingers. In the great toe, the lateral margins of the matrix and nail extend almost halfway around the terminal phalanx. This provides strength appropriate to the foot (Fig. 1.22). The nail appears as a layered structure when examined histologically with silver stain [3], with ultrasound [157], and using optimal coherence tomography [158] or scanning electron microscopy [159]. The different orientation of keratin fibrils within these layers appears to lend characteristics of both toughness and flexibility.

Lewis [3] described a silver stain that delineates the nail plate zones. Three regions of nail plate have been histochemically defined [160] (Fig. 1.21). The dorsal plate has a relatively high calcium, phospholipid, and sulfhydryl group content. It has little acid phosphatase...
### Table 1.5 Analysis of the nail unit basement membrane zone using monoclonal and polyclonal antibodies.

<table>
<thead>
<tr>
<th>Digit 1</th>
<th>Digit 2</th>
<th>Digit 3</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Nail apparatus</strong></td>
<td><strong>Nail apparatus</strong></td>
<td><strong>Nail apparatus</strong></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Fold</strong></td>
<td><strong>Matrix</strong></td>
<td><strong>Bed</strong></td>
</tr>
<tr>
<td>Monoclonal antibody</td>
<td></td>
<td></td>
</tr>
<tr>
<td>LH7:2</td>
<td>+</td>
<td>+</td>
</tr>
<tr>
<td>L3d</td>
<td>+</td>
<td>+</td>
</tr>
<tr>
<td>Co1 IV</td>
<td>+</td>
<td>+</td>
</tr>
<tr>
<td>GB3</td>
<td>+</td>
<td>+</td>
</tr>
<tr>
<td>LH24</td>
<td>+</td>
<td>+</td>
</tr>
<tr>
<td>LH39</td>
<td>+</td>
<td>+</td>
</tr>
<tr>
<td>GDA</td>
<td>+</td>
<td>+</td>
</tr>
<tr>
<td>Tenascin</td>
<td>+</td>
<td>+</td>
</tr>
<tr>
<td>a6</td>
<td>+</td>
<td>+</td>
</tr>
<tr>
<td>G71</td>
<td>+</td>
<td>+</td>
</tr>
<tr>
<td>Polyclonal antibody</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Fibronectin</td>
<td>−</td>
<td>−</td>
</tr>
<tr>
<td>Laminin</td>
<td>+</td>
<td>+</td>
</tr>
<tr>
<td>BP 220kDa</td>
<td>+</td>
<td>+</td>
</tr>
<tr>
<td>EBA 250kDa</td>
<td>+</td>
<td>+</td>
</tr>
<tr>
<td>LAD 285kDa</td>
<td>+</td>
<td>+</td>
</tr>
<tr>
<td>LAD ?kDa</td>
<td>+</td>
<td>+</td>
</tr>
</tbody>
</table>

BP, bullous pemphigoid; EBA, epidermolysis bullosa acquisita; LAD, linear IgA disease.

![Figure 1.22](image.png)

**Figure 1.22** Nail plate association with soft tissue and bone in the finger and toe. (a) In the finger, the nail plate has modest transverse curvature and shallow association with soft tissues. (b) In the great toe, the nail plate has more marked transverse curvature and deep soft tissue association. This makes it appropriate to the foot but also accounts for the tendency to ingrow and the need for deep lateral extirpation at lateral matricectomy.
activity and is physically hard. The phospholipid content may provide some water resistance. The intermediate nail plate has a high acid phosphatase activity, probably corresponding to the number of retained nuclear remnants. There is a high number of disulfide bonds and low content of bound sulfhydryl groups, phospholipid, and calcium. Controversy suggests that the ventral nail plate may be a variable entity [161]. Jarrett and Spearman [160] described it as a layer only one or two cells thick. These cells are eosinophilic and move both upwards and forward with nail growth. With respect to calcium, phospholipid, and sulfhydryl groups, it is the same as the dorsal nail plate. It shares a high acid phosphatase and frequency of disulfide bonds with the intermediate nail plate. Nail plate integrity relies on the relationship of alpha coil and beta pleated sheets of keratin [161]. A combination of total reflection–Fourier transform infrared spectroscopy and X-ray photoelectron spectroscopy demonstrates that in psoriatic nail plate dystrophy the S–S bonds degrade to S–H and sulfite bonds with associated loss of alpha coils, increase in beta pleats random coils, and amorphous protein aggregation. These changes are seen with the loss of nail integrity and correlate with a more disordered incoherent appearance on scanning electron microscopy. In contrast, the disulfide bonds in onychomycosis appear to remain intact although there is disruption of cell–cell interaction and resulting increase in permeability [162].

Ultrasound examination of in vivo and avulsed nail plate suggests that it has the physical characteristics of a bilamellar structure [163]. There is a superficial dry compartment and a deep humid one. This has been given as evidence against the existence of a ventral matrix contribution to the nail plate. Synchrotron X-ray microdiffraction has been used to identify a trilamellar structure, where the dorsal and ventral fibers run transversely and the central fibers run in the longitudinal axis of the nail plate, occupying 70% of nail plate thickness. This laminar thickening enhances nail resistance to tear and fracture forces in multiple axes [164].

The upper surface of the nail plate is smooth and may have a variable number of longitudinal ridges that change with age. These ridges are sufficiently specific to allow forensic identification and the distinction between identical twins [165]. Lyonization studies suggest that there is a sustained pattern of X-inactivation within the progenitor cells of single longitudinal nail ridges [166]. The ventral surface also has longitudinal ridges that correspond to complementary ridges on the upper aspect of the nail bed (see “Nail bed and hyponychium”) to which it is bonded (Fig. 1.23). These nail ridges may be best examined using polarized light. They can also be used for forensic identification [167], as may blood groups from fragments of nail plate [168].

The nail plate gains thickness and density as it grows distally [11] according to analysis of surgical specimens. In vivo ultrasound suggests that there may be an 8.8% reduction in thickness distally [169]. A thick nail plate may imply a long intermediate matrix. This stems from the process whereby the longitudinal axis of the intermediate matrix becomes the vertical axis of the nail plate (Fig. 1.24). Other factors, such as the linear rate of nail growth [170], vascular supply, subungual hyperkeratosis, and drugs, also influence thickness. When comparing the transverse curvature of nails on dominant and non-dominant hands and between occupations with active high mechanical digit use (carpenters) and those with low (secretaries), it appears that the greater use and force applied through pinch strength results in a flatter nail [171]. The same is seen when comparing nails on the hemiplegic and contralateral hand in stroke victims [172]. A simple model in the adult hand is that the dominant hand has flatter nails than the non-dominant, which has been confirmed and is true when comparing men with women. It also holds with age, and power of grip does not always correspond to age and may reduce later in life [173]. A more global theory of forces and nail curvature attempts to explain the extremes of koilonychia and pincer nail through a mix of differential matrix growth and external mechanical molding forces. It requires the nail to be seen as a layered structure where the differences between the rate of movement of the dorsal and ventral nail results in curvature. It does not take
account of some of the underlying bone changes that also contribute to the change of nail shape over time. A mathematical model calculating the forces acting on the nail through adhesion, growth, and nail fold constraint can be used to explain the basis for pincer nails and ingrowing [174].

Transverse curvature and ultimately ingrowing can be influenced by the geometry of the relationship between the preterminal and distal phalanx. This will determine the pattern of forces on the distal and disto-lateral nail edge. Asymmetric forces tend to lead to nail deformity over time such that the risk of an ingrown toenail is greater in someone with hallux valgus [175]. A mathematical model calculating the forces acting on the nail through adhesion, growth, and nail fold constraint can be used to explain the basis for pincer nails and ingrowing [176].

In clinical practice, histology of the nail plate may be useful in a range of settings [177]. These include the diagnosis of psoriasis [178] and identification of fungal infections in culture-negative specimens [40, 46] (Fig. 1.25). It may also be used to identify the dorsoventral location of melanin in the nail clipping of a longitudinal melanonychia and hence allow prediction of the site of melanocyte activity in the intermediate matrix [179, 180]. Sonnex et al. [5] describe the histology of transverse white lines in the nail.

Germann et al. [181] utilized a form of tape stripping in conjunction with light microscopy to examine dorsal nail plate corneocyte morphology in disease and health. They found that conditions of rapid nail growth (psoriasis and infancy) resulted in smaller cell size. Nail keratin protein has been sampled and quantified using a similar tape-stripping method followed by colorimetric quantification [182].

**Electron microscopy**

Scanning electron microscopy has added to our understanding of onychoschizia [183, 184] as well as basic nail plate structure [185, 186]. In the normal nail, corneocytes can be seen adherent to the dorsal aspect of the nail plate. In cross-section, the compaction of the lamellar structure is visible. Both these features can be seen to be disrupted in onychoschizia following repeated immersion and drying of the nail plates. Scanning electron microscopy has also been used for assessing the location of fungal invasion into the nail plate [187, 188], although the lack of differential staining seen in routine light microscopy may mean that the latter is usually more useful.

Transmission electron microscopy has been used to identify the relationship between the corneocytes of the nail plate [91]. Using Thierry’s tissue-processing techniques, material for the following description has been provided. Cells on the dorsal aspect (34 x 60 x 2.2 μm) are half as thick as ventral cells (40 x 50 x 5.5 μm), with a gradation of sizes in between. In the dorsal nail plate, large intercellular spaces are present corresponding to ampullar dilations (Figs 1.26, 1.27). These gradually diminish in the deeper layers and are absent in the ventral region. At this site, cells are joined by complete folds, membranes of adjacent cells appearing to penetrate each other to form “anchoring knots.”

Cell membranes and intercellular junctions are easily discernible (Fig. 1.28). Even though at low magnification one can differentiate the dorsal and intermediate layers

---

**Figure 1.25** Fungal spores and hyphae can be seen in the stained section of a nail clipping taken from a nail with onychomycosis.

**Figure 1.26** (a) Upper part of the nail plate showing ampullar dilatations (A). (b) Lower part of the nail plate showing anchoring knots (K). The only cell-to-cell coupling observed (C) is a desmosome. Courtesy of G. Achten.
of the nail plate, the exact boundary is unclear using transmission electron microscopy. Corneocytes of the dorsal nail plate are joined laterally by infrequent deep interdigitations. The plasma membranes between adjacent cell layers are more discretely indented, often with no invaginations (Fig. 1.28). In the deeper parts of the nail plate, the interdigitations are more numerous but more shallow (Fig. 1.28). No tight or gap junctions are seen in either of the major nail layers in this series [91] although they were identified previously by Forslind and Thyresson [185]. The intercellular material is homogeneous and separated from the cell membrane by two thin electron-dense lines. The space between the cell membranes varies from 25 nm to 35 nm (Figs 1.26–1.28). No complete desmosomal structures are seen.

Nail bed cells show considerable infolding and interdigitation at their junction with the nail plate cells (Fig. 1.29). They are polygonal and show no specific alignment. They are between 6 and 20 µm across and show neither tight nor gap junctions. They do, however, have desmosomal connections of the type seen in normal epidermis (Fig. 1.30).

Cryoelectron microscopy allows examination of fractured intracellular components in great detail without the artefacts normally associated with the chemical processing and coating of traditional electron microscopy techniques. Using this approach, the trichocyte intermediate filaments have been examined in rat vibrissae.

Although these may differ from human nail in some respects, they will share the designation of hard keratins and so allow some transferable observations. The main observation was that the classic keratin fibril structure is the same, but a further arrangement of satellite proteins “decorates” the keratin. These proteins are suspected of
being high sulfur amino acid proteins lending the keratin some of its rugged character [189], possibly through enhancing cross-linking between keratins and increasing their stability [190].

Using different preparation techniques, other workers have demonstrated other anatomical details. On the cytoplasmic side of the cell membranes of nail plate cells lies a layer of protein particles [84, 88, 191]. Other staining techniques suggest that the single type of intercellular bond described by Parent et al. [91] may be a spot desmosome [192].

Vascular supply

Arterial supply

The vascular supply of the finger is considered in detail here (Fig. 1.31). Many of the anatomical principles may be extended to the anatomy of the foot and toe, whilst details can be sought elsewhere [6].

The radial and ulnar arteries supply deep and superficial palmar arcades that act as large anastomoses between the two vessels. From these arcades extend branches aligned with the phalanges. Four arteries supply each digit, two on either side. The dorsal digital arteries are small and arise as branches of the radial artery. They undertake anastomoses with the superficial and deep palmar arches and the palmar digital vessels before passing distally into the finger. The palmar digital arteries provide the main blood supply to the fingers. They receive contributions from the deep and superficial palmar arcades. Although paired, one is normally dominant [193]. They anastomose via dorsal and palmar arches around the distal phalanx. The palmar arch is located in a protected position, beneath the maximal padding of
the finger pulp and tucked into a recess behind the pro-
tuberant phalangeal boss (Fig. 1.31). This is of functional
value as it protects against occlusion of the blood supply
when the fingers exert maintained grip.

The dorsal nail fold arch (superficial arcade) lies just
distal to the distal interphalangeal joint. It supplies the
nail fold and extensor tendon insertion. It is tortuous,
with numerous branches to the intermediate nail matrix.
Its transverse passage across the finger can be roughly
located by pushing proximally on the free edge of the nail
plate. This produces a faint crease about 5 mm proximal
to the cuticle and is both the cul-de-sac of the proximal
nail fold and the line of the dorsal nail fold arch.

The subungual region is supplied by distal and proximal
subungual arcades, arising in turn from an anastomosis of
the palmar arch and the dorsal nail fold arch. Helpful
studies on adults and fetuses have been performed by
Flint [194], Wolfram-Gabel and Sick [107], and Sangiorgi
[114]. The last made use of corrosion casting on cadaver
digits to demonstrate the complex microvasculature.

The tortuosity of the main vessels in the finger is a
notable feature. Vessels may turn through 270° and
resemble a coiled spring [193]. Functionally, this can be
interpreted as protection against occlusion by kinking in
an articulated longitudinal structure.

Venous drainage
Venous drainage of the finger is by deep and superficial
systems. The deep system corresponds to the arterial
supply. Superficially, there exist the dorsal and palmar
digital veins, which are in a prominent branching net-
work, particularly on the dorsal aspect. However, in the
microsurgical techniques needed to restore amputa-
tions, it appears that, distally, the palmar superficial
veins are largest [195].

Although the arterial supply to the nail unit is substan-
tial, the matrix will tolerate only limited trauma before
scarring [97]. A longitudinal biopsy of greater than 3 mm
is likely to leave a permanent dystrophy. Equally, it
appears to need a precise, not just abundant, blood sup-
ply. Non-vascularized split-thickness nail bed grafting is
moderately successful for the nail bed, but not for inter-
mediate matrix [99]. This is in the presence of otherwise
adequate local blood supply at sites of previous trauma.
Toenail matrix grafts can be made successfully if they are
transplanted with associated soft tissue and a venous
pedicle [98]. The local arterial supply is then anastomo-
sed through this pedicle.

Effects of altered vascular supply
Impaired arterial supply can have a considerable effect
upon the finger pulp and nail unit. Lynn et al. [196]
claimed that there was almost complete correlation
between occluded arteriographic findings and the pres-
ence of paronychial infection or ulceration, ridged brittle
fingernails, or phlyctenular gangrene. Samman and
Strickland [197] reviewed the nail dystrophies of 41
patients with features of peripheral vascular disease. In
this uncontrolled study, they observed that onycholysis,
Beau’s lines, thin brittle nails, and yellow discoloration
were all attributable to ischemia in the absence of other
causes. It has also been suggested that congenital onych-
odyplasia may result from digital ischemia in utero [47].
Immobilization might be associated with diminished
local blood supply and has been noted to reduce nail
growth [198]. Conversely, the increased growth associ-
ated with arteriovenous shunts may reflect the role of
greater blood flow [199]. Dynamic tests of blood flow
can be undertaken with infrared thermography to detect
a difference between patients with Raynaud disease and
normal controls following immersion of the hand in cold
water. Both the recovery of normal skin temperature and
the rate of recovery between the proximal nail fold and
eral aspect of the distal interphalangeal joint are
different in those with Raynaud disease following a 10-s
immersion to 10°C [200]. Doppler assessment of the
blood flow in the proximal third of the nail bed in patients
with psoriasis and controls illustrates that those with nail
psoriasis have blood flow resistance. The significance of
this is not clear, but, on a systemic level, psoriasis is
associated with vascular disease through a multifactorial
mechanism and, on a microvascular level, psoriasis
appears related to microvascular pathology [201].
Clipping constitutes a change in both the nail and nail
bed. It is believed that it arises secondary to neurovascu-
lar pathology. Postmortem studies suggest that it is due
to increased blood flow with vasodilation rather than
vessel hyperplasia [202].

Nail fold vessels
The nail fold capillary network [203] is seen easily with
a × 4 magnifying lens, dermoscope [204], or ophthal-
moscope. The latter should be set at +40 and the lens
held very close to a drop of oil on the nail fold. The
network is similar to the normal cutaneous plexus in
health, except that the capillary loops are more hori-
zontal and visible throughout their length. The loops
are in tiers of uniform size, with peaks equidistant from
the base of the cuticle (Figs 1.32, 1.33) [205]. The
venous arm is more dilated and tortuous than the
arterial arm. There is a wide range of morphologies
within the normal population [206]. Features in some
disorders may be sufficiently gross to be useful without
magnification, erythema and hemorrhages being the
most obvious. Toenail nail fold vessels are less informa-
tive than fingernails in a typical pathological state such
as scleroderma [207].
In the first 10 years of life, the pattern of nail fold vessels is immature [208]. Microscopy of small vessels in adulthood can be of diagnostic value in some connective tissue diseases [209, 210]. Pathological features include venous plexus visibility, density of capillary population, avascular fields, hemorrhages, giant capillaries, and cessation of blood flow following cooling. When determined quantitatively, using television microscopy, Studer et al. [211] found it possible to distinguish between systemic and disseminated cutaneous lupus erythematosus, and between localized and systemic sclerosis. In patients with undifferentiated connective tissue disease, it may be possible to predict which will progress to systemic sclerosis by undertaking quantitative analysis of nail fold vessel dimensions. The larger the vessels, the more likely that the condition is going to progress [212–214]. The mechanism of dilated vessel evolution may in part arise from impaired fibrinolysis, macroglobulinemia, and cryoglobulinemia [205].

Fibrinogen may increase in subjects in renal failure on continuous ambulatory peritoneal dialysis. This has been proposed as a cause for the changes seen in nail fold vessels of such patients in proportion to abnormalities of urea and uric acid clearances [215]. Nail fold vessel changes may also occur in psoriasis and appear to correlate with nail pitting, onycholysis, and periungual psoriatic plaques [216]. However, it can be imagined that the clinical or subclinical elements of cutaneous psoriasis may represent the underlying change in vessel pattern.

The capillary networks in the normal nail fold of toes and fingers have been compared using videomicroscopy. This has revealed a greater density of capillaries in the toenail fold but with a reduced rate of flow [217]. The exact pattern of an individual’s nail fold vessels can be used as an identifying characteristic [218].

Intravenous bolus doses of sodium fluorescein dye have been followed through nail fold microscopy [219]. There is rapid and uniform leakage from the capillaries in normal subjects to within 10 µm of the capillaries. It is suggested that a sheath of collagen may prevent diffusion beyond this point. The same procedure has been followed in patients with rheumatoid arthritis, demonstrating decreased flow rates and abnormal flow patterns, but no change in vessel leakage [220]. Static nail fold microscopy has been used for the investigation of Raynaud phenomenon [221]. It is possible to assess vascular toxicity affecting nail fold vessels following chemotherapy, using the same method [222]. A small number of laboratories are also able to employ in vivo capillary pressure measurement for nail fold vessels [223]. Video studies can be used to measure red cell velocity in nail fold capillaries [224], which has been used as a means of quantifying vascular damage in subjects with systemic sclerosis [225]. Systemic sclerosis and other microvascular disorders can be usefully assessed using laser Doppler, which can be combined with videocapillaroscopy for further detail [226].

Ultimately, histological information on the vessels and tissue of the nail folds may be helpful. The technique and benefits of nail fold biopsy have been described [227]. Amyloid deposits, subintimal hyalinosis, and severe dermal fibrosis are cited as useful supplementary information yielded by biopsy.

**Glomus bodies**

A glomus body is defined as a ball, tuft, or cluster, a small conglomeration, or plexus of cavernous blood vessels. In the skin it is an end-organ apparatus in which there is an arteriovenous anastomosis (AVA) bypassing the intermediary capillary bed (Fig. 1.34). This anastomosis includes the afferent artery and the Sucquet–Hoyer canal. The latter is surrounded by structures including cuboidal epithelioid cells and cells possibly of smooth muscle or pericyte origin (Zimmerman type). These are
surrounded by a rich nerve supply and then the efferent vein which connects with the venous system outside the glomus capsule.

The nail bed is richly supplied with glomus bodies and their presence in histological specimens should be interpreted in this context, rather than assuming that their abundance has some pathological significance. These are neurovascular bodies which act as AVAs. AVAs are connections between the arterial and venous side of the circulation with no intervening capillaries. Each glomus body is an encapsulated oval organ 300 µm long composed of a tortuous vessel uniting an artery and venule, a nerve supply, and a capsule. It contains many modified large muscle cells, resembling epithelioid cells, and cholinergic nerves. Digital nail beds contain 93–501 glomus bodies per cm³. They lie parallel to the capillary reservoirs that they bypass. They are able to contract asynchronously with their associated arterioles such that, in the cold, arterioles constrict and glomus bodies dilate. They can thus serve as regulators of capillary circulation, acquiring the name “the peripheral heart of Masson” [228]. They are particularly important in the preservation of blood supply to the peripheries in cold conditions.

Nerve supply

The periungual soft tissues are innervated by dorsal branches of paired digital nerves. Wilgis and Maxwell [229] stated that the digital nerve is composed of three major fascicles supplying the digit tip, with the main branch passing under the nail bed and innervating both nail bed and matrix [230]. Winkelmann [231] showed many nerve endings adjacent to the epithelial surface, mainly in the nail folds. Serial dissections of cadaver
hands demonstrate that there is often dual sensory innervation of the nail unit on the dorsal aspect of the digit, which is relevant when attempting anesthesia with ring block [232] (Fig. 1.35).

**Comparative anatomy and function**

The comparative anatomy of the nail unit can be considered from two aspects. There is the comparison of the nail with other ectodermal structures and most particularly hair and its follicle. The nail can also be viewed in an evolutionary setting alongside the hoof and claw. In this respect, the functional qualities of the nail or its equivalent are exemplified by the morphological differences in different species.

The human nail can be considered to have many mechanical and social functions, the most prominent of which are:
- fine manipulation
- scratching
- physical protection of the extremity
- as a vehicle for cosmetics and esthetic manipulation.

In comparison with other species, the first three functions have evolved with detailed physical modifications in the form of the hoof, claw, and nail.

**The nail and other appendages**

An appendage is formed through the interaction of mesoderm and ectoderm, which in differentiated states usually means the interaction between dermis and epidermis. Those appendages most closely related to nail include hair and tooth. There are many shared aspects of different appendages, illustrated by diseases, morphology, and analysis of the biological constituents (Figs 1.36, 1.37).

Congenital abnormalities of hair, tooth, and nail coexist in several conditions, underlining their common ground. Ectodermal dysplasias represent a group of disorders in which these appendages, as well as eccrine sweat glands, may be affected in association with skin changes.

In some conditions, only two of the appendages seem to be affected, such as the hair and nail changes described by Barbareschi et al. [233] or tooth and nail changes in the hypodontia and nail dysplasia syndrome (Witkop tooth and nail syndrome) [234, 235]. Alternatively, the
same genetic defect, such as a mutation in the gene for K17, may underlie two separate diseases where the nail is abnormal in one phenotype and the hair follicle in the other [236]. Presumably an additional factor determines which of the possible phenotypes prevails.

While diseases illustrate interrelationships between appendages, further common ground can be defined in terms of morphology. Achten [237] noted that the nail unit was comparable in some respects to a hair follicle, sectioned longitudinally and laid on its side (Fig. 1.37). Perrin [115] has also described the area between the nail bed and hyponychium as the nail isthmus, to emphasize the resemblance to the isthmus of the hair follicle. The hair bulb was considered analogous to the intermediate nail matrix and the cortex to the nail plate. As a model to stimulate thought, this idea is helpful. It also encourages the consideration of other manipulations of the hair follicle that might fit the analogy more tightly. The nail unit could be seen, as in Fig. 1.36, as an unfolded form of the hair follicle, producing a hair with no cortex, just hard cuticle. Scanning electron microscopy of the nail confirms that its structure is more similar to compacted cuticular cells than cortical fibers. A third model could represent the nail unit as a form of follicle abbreviated on one side, providing a modified form of outer root sheath to mold and direct nail growth in the manner of the proximal nail fold. The matrix and other epithelial components of tooth can be seen in a similar comparative light and even the lingual papilla, which shares some keratin expression with the nail, shows some morphological similarities to the nail and hair follicle [152].
In pachyonychia congenita where alopecia is found, transverse sections of scalp follicles reveal dyskeratosis of the outer root sheath, attracting comparisons with the nail bed [238]. In some diseases the immunological focus is shared between the nail matrix and hair follicle, as in lichen planus and alopecia areata. This suggests common ground in immunological identity, which could be related to specific keratins. Ito et al. [239] described a pattern of relative immune privilege in the proximal nail matrix similar to that seen in the hair follicle which might normally play a part in blocking the autoimmune attention of white cells. Defects in this could open the way to a common path and manifestation of disease (Fig. 1.37).

The character of the nail plate and hair has led to their use in assays of circulating metabolites. They both lend themselves to this because they are long-lasting structures that may afford historical information. Additionally, their protein constituents bind metabolites and they provide accessible specimens. This allows both hair and nail to be used in the detection of systemic metabolites which may have disappeared from the blood many weeks previously (see “Exogenous materials in nail analysis”).

**Phylogenetic comparisons**

The structure of claws and hooves and their evolutionary relationship to the human nail have been well reviewed [240]. In higher primates, nails have developed with the acquisition of manual dexterity. Other mammals do not possess such flattened claws from which nails have evolved (Figs 1.38, 1.39). Mouse claw anatomy has sufficient common ground with human nail to allow use as a model of human ungula biology [126] (Figs 1.40, 1.41).

The lowest evolutionary level at which claws are seen is in the Amphibia [241]. The matrix contributes the greatest mass to the nail plate in humans and other primates, with a lesser contribution from the dorsal and nail bed matrices. Claws are formed from an extensive germinial matrix, which occupies the territory of the nail bed in primates [242]. It is sometimes described as comprising a dorsal and ventral component [243], where differential growth of these components is responsible for the curve. The orientation of the matrix and hence growth of nail may be influenced by the shape of the underlying phalanx [242]. It is postulated that their sharp tip is produced by a dominant midline matrix.

Claws are significantly more three dimensional than nails, and this is achieved by the coronal distribution of matrix tissue around the terminal phalanx. If this is recognized, the comparisons between other hard keratinized animal appendages such as horns and beaks become obvious. All these structures share physical and biochemical attributes specific to their biological character and function. In some respects, the upper beak has more in common with the morphology of the nail than

---

**Figure 1.38** Comparison of hoof, nail, and claw and their matrix (red) origins.
do claws, and comparisons have been made in both structure and constituents between beak and claw [244]. The disorders of claws presenting to one university veterinary service demonstrated a preponderance of trauma and bacterial infection [245] (Table 1.6). This differs from dermatological experience in humans where complaints are usually attributable to dermatoses such as psoriasis or eczema or to fungal infection.

Claws and talons are harder than nails, probably because of the content of calcium as crystalline hydroxyapatite within keratinocytes (cf. human nails) [246]. A study of onychomadesis (nail shedding) in dogs looked at mineral constituents of normal claws, human nails, and the hooves of cows and pigs [247]. It appears that there is no particular pattern of homology between different species in this respect (Table 1.7).

Keratin immunohistochemistry for epithelial and hair/nail keratins has made it easier to identify the types of keratins found in animal appendages. Such studies illustrate substantial homology between the canine claw, mouse, and human nail [126, 248] (Figs 1.41, 1.42) and, to a lesser extent, similarities with the reptilian claw [249]. The anatomy of the equine hoof allows comparison with human nails but there are also substantial differences, including the presence of some keratins, K42 and K124, not found in human tissue [250]. In some instances, animal mutants have helped corroborate the role of a specific keratin in the human phenotype. Mice with mutation of the gene expressing K75 (K6hf) demonstrate features similar to humans with pachyonychia congenita where the human K75 gene is also known to be at fault [251].

Orientation of keratin microfibrils may contribute to their strength. Fourier-transform Raman spectroscopy shows that bird and reptile claws are made up mainly of β-sheeted keratin in contrast to the predominantly α-helical keratin conformation of human nail keratin [252].

Claws and nails have more in common with each other than they do with hooves. However, the bovine hoof has provided a useful source of research tissue for experiments on colocalization of hard and soft keratin expression in matrix cells and the characteristics of matrix cells in tissue culture [134]. Hooves have evolved to provide a “bulky claw” for weight bearing and locomotion over hard ground [253]. It is interesting that, among the prosimians, tarsiers have nails on all digits apart from the second and third digits of the hindlimbs, which bear claws [240]. In hooves, the nail fold and root
Figure 1.40 Light microscopy of the nail unit. The human nail unit (a–f). (a) Sagittal section through the distal part of a human newborn digit. (b–f) Higher magnification of the boxed areas in (a). (a) The nail plate (np) covers the dorsal surface of the distal digit and extends over its free edge. The nail plate invaginates proximally into the proximal nail fold (pnf). The regions of nail matrix (nm), nail bed (nb), and hyponychium (hn) are marked by square brackets. The cuticle (cu) (a,b) is a layer of cornified cells that attaches to the dorsal surface of the nail plate and is produced by keratinocytes of the tip of the proximal nail fold and the eponychium (en), the epithelium covering the ventral surface of the proximal nail fold that shows a prominent granular layer but no papillae (b, insert). At the blunt, free end of the nail plate (a,f) cornified layers of the hyponychium are attached to the under surface of the nail plate. The nail matrix (c,d) is represented by a thickened epithelium at the base of the nail plate starting at the point where the eponychium with its granular layer ends (c, arrow), extending distally to the nail bed which is marked by reduction of cell layers (d, arrowhead). The hyponychium starts where the nail detaches from the nailbed, visible by the appearance of a granular layer (e, arrow). It extends to the distal groove (dg) (a). (a) Bar = 1 mm; (b–f) bars = 100 µm. The mouse nail unit (g–l). (g) Sagittal section through the distal part of an adult mouse nail unit. (h–l) Higher magnification of the boxed areas in (g). The regions of nail matrix (nm), nail bed (nb), and hyponychium (hn) are marked by a continuous, dotted, and dashed line, respectively. Arrows in (c,e,i,k) indicate the onset of the granular layer; (h) shows the eponychium (en) that contributes to the cuticle (cu). Insert in (i) shows a higher magnification of the boxed area with the loss of the granular layer at the transition to the apical matrix (am). Arrow tip in (i) indicates loss of the granular layer (onset of onycholemmal keratinization) at the transition from nail matrix to nail bed. Arrow tip in (k) indicates reappearance of the granular layer at the transition from nail bed to hyponychium. (g) Bar = 500 µm; (h–l) bars = 100 µm; (i, inset) bar = 50 µm. Reproduced from Fleckman et al. [126] with permission of John Wiley and Sons.
Figure 1.41 Keratin expression in the mouse nail unit. Longitudinal sections through the mouse nail unit were labeled with antibodies against KRT5 (a,g), KRT14 (b,h), KRT17 (c,e,i), KRT6A (d,f,j), KRT1 (k,l), KRT10 (m,n), and acidic hair keratins detected with the monoclonal mouse antibody AE13 (o, o'). (a–e,k,m,o) The proximal aspect of the nail unit including apical matrix (am), ventral matrix (vm), eponychium (en), and nail plate (np). (g–j,l,n) The distal aspect of the nail unit consisting of the nail bed (nb) and the hyponychium (hn). KRT5 (a), KRT14 (b), and KRT17 (c) show a very similar pattern in the nail matrix and the eponychium. However, KRT17 is often detectable only in occasional cells in the distal matrix (c, inset) and in limited areas of the hyponychium (l). KRT6A (d) is expressed in the apical matrix but not in the ventral matrix. (e,f) A higher magnification of the nail bed where suprabasally located KRT17 (e) and KRT6A (f) positive cells (arrowheads) were detectable. (g) The basal expression of KRT5 in the hyponychium, whereas K14 (h) shows a panepidermal pattern. Note the patchy pattern of KRT17 (i) in the same region. (j) KRT6A shows panepidermal labeling of the hyponychium. KRT1 labeling in the proximal (k) and distal (l) nail unit shows a strong panepidermal expression of the eponychium and suprabasal expression of the hyponychium but no labeling of nail matrix or nail bed. Note that the apical matrix also shows basal labeling (k, inset) and that in the hyponychium the labeling reaches some areas in the basal layer (l, inset). KRT10 shows a pattern similar to that of KRT1, but less extension to the basal layer (m,n, insets). AE13 labeling illustrates the expression of hard keratins in the suprabasal layers of the nail matrix (o, o'). np, nail plate. Dashed lines, border between dermis and epidermis. Bars = 50 µm Reproduced from Fleckman et al. [126] with permission of John Wiley and Sons.

Table 1.6 Proportion of diagnoses of dogs with disorders of the claws from a study of 196 affected dogs.

<table>
<thead>
<tr>
<th>Diagnosis</th>
<th>% of cases</th>
</tr>
</thead>
<tbody>
<tr>
<td>Bacterial paronychia</td>
<td>35.5</td>
</tr>
<tr>
<td>Trauma</td>
<td>22</td>
</tr>
<tr>
<td>Neoplasia</td>
<td>14</td>
</tr>
<tr>
<td>Fungal</td>
<td>4</td>
</tr>
<tr>
<td>Lupoid</td>
<td>4</td>
</tr>
<tr>
<td>Bullous disorder</td>
<td>4</td>
</tr>
<tr>
<td>Demodicosis</td>
<td>1</td>
</tr>
<tr>
<td>Systemic illness</td>
<td>0.5</td>
</tr>
<tr>
<td>Idiopathic</td>
<td>15</td>
</tr>
</tbody>
</table>

Adapted from Scott and Miller [245].

Table 1.7 Mineral content (expressed as mg/kg, standard error in parentheses).

<table>
<thead>
<tr>
<th>Mineral</th>
<th>Dog claw</th>
<th>Porcine hoof</th>
<th>Bovine hoof</th>
<th>Human nail</th>
</tr>
</thead>
<tbody>
<tr>
<td>Calcium</td>
<td>771 (83)</td>
<td>1699 (50)</td>
<td>1481 (25)</td>
<td>671 (806)</td>
</tr>
<tr>
<td>Magnesium</td>
<td>238 (21)</td>
<td>220 (10)</td>
<td>300 (11)</td>
<td>100 (121)</td>
</tr>
<tr>
<td>Iron</td>
<td>268 (31)</td>
<td>73 (8)</td>
<td>17 (1.1)</td>
<td>29 (64)</td>
</tr>
<tr>
<td>Potassium</td>
<td>430 (53)</td>
<td>1050 (30)</td>
<td>785 (53)</td>
<td>–</td>
</tr>
<tr>
<td>Sodium</td>
<td>676 (50)</td>
<td>–</td>
<td>523 (16)</td>
<td>2400 (1800)</td>
</tr>
<tr>
<td>Copper</td>
<td>6.3 (0.5)</td>
<td>4.6 (0.13)</td>
<td>8.3 (0.3)</td>
<td>29 (89)</td>
</tr>
<tr>
<td>Zinc</td>
<td>129 (5)</td>
<td>160 (4)</td>
<td>128 (1.7)</td>
<td>106 (154)</td>
</tr>
</tbody>
</table>

Adapted from Harvey and Markwell [247] with permission from Wiley Blackwell.
have been displaced backwards with a forwards extension of the nail bed. The hard “soft plate” under hooves is produced from an area equivalent to the subungual part of the claw. In some animals, cloven hooves have only developed on the digits that touch the floor. In horses, the single large hoof is produced from the third digit. The typical hoof shape is due to a deep, backwardly placed root matrix with the ventral plate formed from the subungual epidermis. The microfibrils in hooves are from 25 to 100 nm in diameter. The orientation of the fibrils is along the main axis of the hoof, similar to the hair cortex. The parallel ridge pattern seen longitudinally in the human nail bed is prominent in hooved animals such as horse. Longitudinal growth rate is similar in all mammals in which it has been assessed: between 0.1 and 0.3 mm/day [176].

Physiology

Nail production

Definition of the nail matrix

In the first section, we have attempted to define the matrix in anatomical terms, assisted by histology and immunohistochemistry illustrating regional differentiation within the nail unit and in particular with respect to keratin expression. These measures provide indirect information on aspects of nail production and help us to address the central question of which tissues produce nail plate and which simply support and surround it. There is considerable biological and clinical relevance to this point, given that the focus of embryogenesis, damage repair, and disease processes is better understood if the exact location of nail formation is established.

The location or existence of nail matrix tumors is often poorly defined because there is a lack of awareness of the site and pivotal role of nail matrix disturbance in the creation of abnormal nail morphology. Equally, diagnostic biopsies or sampling can be misdirected if the likely source of nail abnormalities is not recognized at the outset; a clear prognosis following surgery or trauma cannot be given unless the clinician understands the relative contributions of the nail matrix and nail bed.

In spite of the importance of the question, controversy remains as to the relative contributions of the three putative nail matrices to the nail plate. The three contenders are the dorsal, intermediate, and ventral matrices (Fig. 1.43). The first is part of the proximal nail fold, the last is the nail bed. Lewis [3] claimed that the nail plate demonstrated a three-layer structure on silver staining and that each layer derived from one of the possible matrices. This remains one of the indirect histological methods of defining the matrix which have been supplemented by more direct measures of nail plate production.
Markers of matrix and nail bed proliferation
Zaias and Alvarez [11] disagreed with Lewis on the basis of in vivo autoradiographic work on squirrel monkeys, where dynamic aspects of the process were being examined. Tritiated thymidine injected into experimental animals was only incorporated into classic matrix (or intermediate matrix, to use Lewis’s terminology). Norton [254] used human subjects in further autoradiographic studies. Although there was some incorporation of radiolabeled glycine in the area of the nail bed, it was in a poorly defined location, making clear statements impossible.

Immunohistochemical techniques allow us to examine proliferation markers in human tissue, without the drawbacks of autoradiography. Antibodies to proliferating cell nuclear antigen and to the antigen Ki-67 associated with cell cycling have been used on longitudinal sections of healthy and diseased nail units [125, 255]. Both markers demonstrate labeling indices in excess of 20% for the nail matrix, in contrast with 1% or less for the nail bed in healthy tissue. The differences are less marked according to Perrin [125], with an index of 21% in the matrix and 5% in the nail bed. In psoriatic nail and onychomycosis, the labeling index of nail bed rises to >29%. While these indices do not directly measure nail plate production, a very low index for normal nail bed is consistent with other studies, suggesting that the nail bed is an insignificant player in normal nail production. The situation may change in disease and the definition of nail plate becomes difficult when substantial subungual hyperkeratosis produces a ventral nail of indeterminate character [256].

Nail plate indicators of matrix location
Johnson et al. [12, 257] dismissed the evidence of Zaias, claiming that the methodology was flawed. They examined nail growth by the measurement of change in nail thickness along a proximal to distal longitudinal axis. They demonstrated that 21% of nail plate thickness in traumatically lost great toenails was gained as the nail grew over the nail bed. This was taken as evidence of nail bed contribution to the nail plate.

A similar study developed this observation with histology of the nail plate taken at fixed reference points along the longitudinal nail axis and comparing nail plate thickness at these sites with numbers of corneocytes in the dorsoventral axis of the nail [101]. The result of this was to confirm the observation that the nail plate thickens over the nail bed but that this is not matched by an increase in nail cells. In fact, the number of cells reduces by 10%, but this was not of statistical significance. These combined studies may be reconciled if we propose that the shape of cells within the great toenail becomes altered with compaction as the nail grows. This is likely where clinical experience shows that the nail develops transverse rippling when there is habitual distal trauma.

If the loss of nail cell numbers along the nail bed is a genuine observation, it might suggest that cells are being shed from the nail surface. This is compatible with the status of nail plate as a modified form of stratum corneum. Heikkilä et al. [258] provide evidence in support of this where nail growth was measured by making indentations on the nail surface and measuring the change in the volume of these grooves as they reach the free edge. There was a reduction of volume by 30–35%, which was taken as evidence of a nail bed contribution to the nail plate. However, this interpretation is less believable than the possibility that the nail is losing cells from the surface, and histology of grooves in a similar study shows that this is likely to be the case [259].

Flow cytometry of matrix cells
Haneké and Kiesewetter (unpublished data) have performed flow cytometry on matrix cells obtained during surgical lateral matricectomy for ingrowing nail. This demonstrated that 94% of the matrix cells were in G0/1 phase, 3.4% in S phase, and 2% in G2 + M phase. The corresponding values for matrix connective tissue cells were 96.6% for G0/1, 2.3% for S, and 1.1% for G2 + M phases. The differences between matrix cells and associated connective tissue were statistically significant. This suggests that the percentage of cells in the phase of DNA synthesis and mitosis (S plus G2 + M phases) in the nail matrix is much lower than that of hair matrix cells and equals that of the cells in the hair root sheath. However, the values may have been underestimated in this experiment if the matricectomies failed to sample the most basal matrix cells, as can happen in this operation. Also, this technique was not applied to distinguish nail bed from matrix and does not directly address the issue of which tissues are primarily involved in nail plate production.

Clinical markers of matrix location
The clearest demonstration of nail generation is the effect of digit amputation at different levels. Trauma within the
lunula is more likely to cause irreparable nail changes than that of the nail bed [260]. This observation is true for adults and children alike, although the likelihood of normal regrowth is greater in children with similar trauma [261]. Longitudinal biopsies of the entire nail unit within the midzone of the nail are said to cause a chronic split if the width of the biopsy exceeds 3 mm [97]. However, there are several factors in addition to the width of the biopsy that can contribute to scarring with longitudinal biopsies and smaller biopsies in the midzone can also give long-term problems.

In some circumstances, most commonly old age, there is a pattern of subungual hyperkeratosis associated with nail thickening that gives the impression of a nail bed contribution to the nail plate. Historically, this has been referred to as the solenhorn (Fig. 1.44) and considered a germinal element of the hyponychium. Samman [256] considered this issue in the context of a patient with pustular psoriasis and concluded that the ventral nail is a movable feast, manifesting itself in certain pathological circumstances.

**Normal nail morphology**

The main issues in normal nail morphology are: why is it flat and why is the free edge rounded and not pointed? Factors influencing nail plate thickness are dealt with earlier (see “Nail plate”).

**Why does the nail grow out straight?**

The first question was addressed in an article by Kligman [262] entitled “Why do nails grow out instead of up?” His hypothesis was that the proximal nail fold acts to mold the nail as it moves away from the matrix, giving an oblique growth path. From observing other keratinizing epithelia, he noted that growth is normally parallel to the axis of keratinization. From this, he considered it anomalous that nails grow out along the nail bed and not upwards (Fig. 1.45). A patient with the nervous habit of chewing off the proximal nail fold did not provide an adequate experiment to demonstrate its function. However,
when given the opportunity to autograft 5-mm matrix punch biopsies from digit to forearm, nail tissue was seen to grow upwards like a cutaneous horn. This was presented as proof of the hypothesis.

Baran [263] was in disagreement and presented evidence from surgical experience in the removal of the proximal nail fold and the lack of subsequent change in the nail. He also challenged the validity of Kligman’s experiment on the basis that the underlying terminal phalanx has a great influence upon nail growth [50] and this was lost in transplanting the graft to the arm.

Since this debate, BMP has emerged as part of the TGF-β family of mediators. It is found in many different forms with a range of morphogenetic roles. In relation to the formation of the nail unit, it has been proposed that there is a two-way process whereby it is supportive of nail unit development, but equally that the nail unit plays a part in the regeneration of the distal phalanx when it is lost through trauma in infancy [43], and these processes may in part be mediated through BMP4.

Further examples of ectopic nail growth still leave room for disagreement [264] and the relevance of acquired bone and nail changes occurring in tandem has its own literature. Carpal tunnel syndrome can result in abnormal nails alongside acroosteolysis and ischemic skin lesions [265]. The reversal of many of the skin and nail features on treatment of the carpal tunnel compression suggests a neurovascular origin to both nail and bone changes in this pattern of acroosteolysis. Where the etiology of the osteolysis is termed idiopathic, there are also nail changes [266]. It seems unlikely that these cases represent a specific influence of bone upon nail formation, but rather that both structures are responding to some undefined agent. There is a wide range of primary disorders in which secondary osteolysis and altered nails are recognized complications [266].

All the models demonstrating the influence of the different periungual tissues and bone upon the nail are flawed. Those above do not acknowledge the adherent quality of the nail bed as an influential factor, or the guiding influence of the lateral nail being embedded in the lateral nail folds. The role of the nail bed becomes manifest in psoriasis affecting the toes where the combination of subungual hyperkeratosis and trauma can produce upward-growing nails in the presence of an apparently normal proximal nail fold. It is reasonable with our present knowledge to consider horizontal nail growth as being attributable to more than one part of the nail unit (Fig. 1.46).

**What determines the contour of the free edge?**

The second issue is why are nails rounded and not pointed? This has generally been accepted as being a function of the shape of the lunula, as illustrated in Fig. 1.47. The mechanism of this is seen in Fig. 1.46. Given that nails are growing continuously throughout life, it is possible to...
argue that we rarely see the true free edge but rather observe the eroded or manicured outline. However, there are two instances when we see the genuine free edge: at birth and with regrowth following avulsion (Fig. 1.48). These appear to follow the margin of the lunula. Finally, the nail bed may have some role in determining the shape of the free edge. Trauma to the nail bed can result in nail plate dystrophies, giving the free edge a scalloped contour. This can be corrected with nail bed grafts [99].

**Nail growth**

**Measurement**

The literature on nail growth has relied on quantification. A range of methods has been employed, mostly requiring the imprint of a fixed reference mark on the nail and measuring its change in location relative to a fixed structure separate from the nail after a study period. Gilchrist and Dudley Buxton [267] made a transverse scratch about 2 mm from the most distal margin of the lunula. This distance was then measured using a rule and magnifier. Changes in the distance with time provided a record of growth rate. There have been variants of this, with the scratch being made at the convex apogee of the lunula and subsequent measurements made with reference to the lunula [268] or, alternatively, making a scratch a fixed 3 mm from the cuticle and noting the change with time [269] (Fig. 1.49). The precision of these methods was increased by the introduction of magnified photographs before and after, and comparison of the photographs [270]. This was modified further by Sibinga [271], who increased the photographic magnification from a factor of 6 to 35. This made it possible to conduct studies of nail growth over a period as short as 1 month.

Babcock [270] understood the problems in the methods involving the lunula and cuticle as reference points, as they both might conceivably change during the study. The method suggested for overcoming this was inventive, but unacceptable these days for ethical reasons. The nail was marked with a deep scratch which was then filled with bismuth amalgam. This made it radiopaque and allowed comparison with the underlying bony reference points on radiographs. A follow-up radiograph, after refilling the scratch with amalgam, allowed growth estimation. The concern over variation in the non-nail plate reference point can be partly surmounted by using two reference points and possibly halving the error. This can be done by making a scratch or laser incision [272] at the tip of the lunula and measuring the distance to the

![Figure 1.48](image-url) T-shaped mark etched on nail for nail growth measurement. From Dawber [269]. Arrow points to posterior nail fold reference point. Note the absence of a cuticle. Courtesy of R. Dawber.

![Figure 1.49](image-url) Methods of nail growth measurement. (a) Reference point, cuticle. Growth = B – A. (b) Reference point, lunula. Growth = B.
(c) Reference point, lunula. Growth = B – A. (d) Reference point, cuticle and nail attachment margin. Growth = (B’ – A’) + (A’ – B’)/2; verification by A’ + A” = B’ + B”.
(e) Reference point, bone. Feature on a radiograph with bismuth amalgam in the nail scratch. Growth depends on landmark.
distal limit of the nail plate attachment, visible through the nail plate. Subsequent measurements are made from both the lunula and the edge of nail plate attachment. Their sum should always be equal as a way of verifying the method (Fig. 1.50).

Surface imaging of the nail, exploiting natural irregularities, can be used in lieu of marks placed by the observer. This has been reported by de Doncker and Piérard [273] in a study of nail growth during itraconazole therapy. The technique was not pushed to its full potential, as only clippings and not the entire in vivo nail plate were assessed. It was thought that longitudinal nail growth increased during therapy because surface beading became more spaced apart.

All these methods involve estimation of linear growth. As a measure of total matrix activity, this could be misleading. Hamilton et al. [274] sought to measure volume by the following equation:

\[
\text{volume} = \text{thickness (mm)} \times \text{breadth (mm)} \times \text{length grown per day}
\]

Johnson et al. [12] also tried to measure volumetric growth with respect to linear growth, ignoring time. This entailed the measurement of thickness and mass at different points in the avulsed nail plate. The method presumed that linear measurements in the longitudinal axis of the nail plate were proportional to time and that no element of compaction complicated the issue.

Attempts to measure volume take on particular significance in disease states provoking Beau’s lines. In a condition where the bulk of the nail is manifestly affected, measurement of linear growth alone may give misleading results (Fig. 1.51).

Measurement of the longitudinal rate of growth may have some bearing on interpretation of studies where the concentration of incorporated elements of compounds is being evaluated. The relevance of the nail growth rate depends on the relative influence of solubility of the compound in the nail and the rate of transfer to the nail. If the rate of nail growth is high and the solubility is low, then it may be a determinant. However, in most instances, it is likely that solubility will be sufficient to allow equilibration between the nail and nail bed before the nail grows out. This may not fully apply to a thick nail, where there may be a limit to the diffusion of the compound upwards through a thick nail. These considerations are covered in the topic of measurement of fluoride in nail as part of studies to look at public health policies of fluoridation for dental care [275, 276].

**Physiological factors and nail growth**

Most studies concern fingernails, whose rate of growth can vary between 1.9 and 4.4 mm/month [271]. A reasonable guide is 3 mm/month or 0.1 mm/day. Toenails are estimated to grow around 1 mm/month. A study of healthy students on a US campus reported values of 3.5 mm/month for fingernails and 1.6 mm/month for toenails [277]. The authors concluded that this represented a
genuine increase over historical controls and may correspond to other biometric increases over the last 30 years. Population studies on nail growth have given the general findings that there is little marked seasonal change and nails are unaffected by mild intercurrent illnesses [268, 271]. The height or weight of the individual made no significant difference [268, 278]. Gender has been thought to make a small difference in early adulthood, with men having significantly ($p < 0.001$) faster linear nail growth up to the age of 19 [274]. They continue to do so with gradually diminishing significance levels, up to the age of 69, when there is a cross-over and women's nails grow faster than men's. However, this pattern may have changed, with apparent equivalence between men and women with more recent analysis [277]. There is rough agreement from Hillman [268] in an earlier study, although he found that the cross-over age was around 40. However, males continued to have a greater rate of nail growth throughout life if volume was measured and not length [274]. Children under 14 have faster growth than adults.

Pregnancy may increase the rate of nail growth [278] and poor nutrition may retard it [231].

Temperature is an influence with unclear effects. Bean [279] kept a slightly idiosyncratic record of his own fingernail growth by making a scratch at the free edge of his cuticle on the first day of each month for 35 years. His record showed a gradual slowing with age. It initially showed a seasonal variation, with heightened growth in the warm months. This variation became less marked with age, combining with a move from Iowa to Texas where seasonal contrasts are reduced. Other studies to determine the influence of temperature have compared nail growth rates for people in temperate and polar conditions. An original study in 1958 [280] found that nail growth was significantly retarded by living in the Arctic. Subsequent studies from the Antarctic found that there was no change in nail growth [281, 282]. These studies are not scientific and it is unclear whether they are commenting on the improvement in thermal insulation since 1958 or nail physiology.

**Nail growth in disease [283]**

**Systemic disease**

Insufficient numbers of seriously ill people have been followed as part of a larger study to give good statistical evidence concerning the influence of disease on nail growth. There is plenty of evidence from small numbers that some severe systemic upsets disturb nail formation. The observations of Justin Honoré Simon Beau in 1836 [284] detailed the development of transverse depressions upon the nails of people surviving typhoid. The form of nail growth interference represented by Beau’s lines is seen in many conditions (see Chapter 2). Yellow nail syndrome can be manifested as a systemic illness of the respiratory system and nails or be seen mainly limited to the nails. In the latter, the clinical features of thickening with yellow discoloration correspond to a reduction in the rate of longitudinal growth. But this can be compensated for in some instances by an increase in nail thickness, with the consequent observation that “the nail that grows half as fast grows twice as thick” [285]. This may not be applicable to all situations, as it has been noted that biotin may reduce nail fragility and at the same time increase both the thickness and rate of longitudinal growth [286]. Severe illness in the form of mumps has been noted to bring linear growth to a standstill [271]. Other acute infections are quite variable, with 10 cases of acute febrile tuberculosis failing to have significant effect [271]. In the same study, chronic nephrosis produced exceptionally slow nail growth. Paradoxically, these authors also found that cadavers appeared to continue the growth of their nails in the 10 days post mortem during which they were assessed. The effect of death was less marked than that of mumps, something adults with mumps might agree with.

**Local disease**

Local diseases can influence nail growth. Dawber et al. [287] noted that onycholysis was associated with increased nail growth. This was true whether it was related to psoriasis or idiopathic. It is interesting that psoriasis may also produce Beau’s lines and so reduce the bulk of the nail. It is not even clear whether Beau’s lines represent a reduction in linear growth. They have been noted after retinoid therapy and yet this group of drugs has also been noted to increase nail growth in psoriasis [288]. The surface morphology of the nail in a Beau’s line reflects a change in rate of nail plate production in different zones in the matrix and a loss of coordination with longitudinal growth; it is a product of pathology in space and time. Perhaps a nail that is growing faster is unable to accumulate bulk. Other systemic psoriasis treatments may reduce the rate of nail growth [289].

Trauma may increase nail growth, onychophagia [277] and wrist fractures being the most common examples. Details of nail and local hair growth have been recorded in instances of reflex sympathetic dystrophy where Beau’s lines and hypertrichosis on the dorsum of wrist, arm, and hand may coincide. It is not clear whether the nail changes represent increased or decreased growth in these circumstances. Hypertrichosis indicates an extension of anagen, such that hairs that might normally fall out at 5 mm or less become longer and may gain a greater diameter. It does not necessarily mean that the hairs are growing faster and so, in common with Beau’s lines, it represents a change in the pattern of appendage growth rather than a simple alteration of rate.

Immobility alone may result in a reduction in the rate of nail growth and, while this factor prevails after wrist fracture, reflex sympathetic dystrophy entails significant changes in blood supply that may have their own effects.
Studies of right/left comparison with onychomycosis of the toenail indicate that there is a reduction in the longitudinal rate of growth of the toenail while it is infected with fungus, which normalizes on cure [272]. In some instances this has been attributed to the effects of the drug itself, terbinafine [290] and itraconazole [273].

Table 1.8 includes influences upon nail growth that are reported, but not always of statistical significance.

### Nail plate biochemical analysis

#### Methods of analysis

A great range of methods has been used to analyze the organic and inorganic content of nails. Table 1.9 gives a guide, indicating how particular methods are appropriate for different constituents. Nail proteins are structural, but the other components are usually deposited within the nail as part of a normal or pathological process reflecting the biological environment of the nail, which in turn will reflect the external environment of the individual. Interpretation of the concentration of biomarkers in nail may require knowledge of the rate of growth of the nail, although the contribution of this variable is not always easy to calculate [291].
Chapter 1

The virtue of nail as a medium for analysis is the manner in which it evens out short-term variations. Consequently, urine may be a good measure for a short-term exposure in the previous 24 h, hair over previous months depending on length, but nail may be useful for periods of over a year where toenails are used. For longer periods still, dental material can be used [292]. These figures are likely to be subject to the length of the hair, the site of nail sampling (toe versus finger), and the age of the subject.

Nail proteins

From Table 1.9 on analytical methods, it is clear that a considerable number of endogenous and exogenous materials can be sought in the nail plate. The protein mesh into which the elements fit is made primarily of the intracellular protein keratin. The highly ordered structure of the proteins in the nail plate helps explain the degree of chemical and physical resistance in contrast to the characteristics of skin. The proteins of hair and nail alike have extensive folding maintained by extremely stable disulfide bonds. Although these bonds can also be found to a lesser extent in the stratum corneum of normal skin, they have a different geometry in the two sites as demonstrated by Raman spectroscopy. This is expressed as gauche–gauche–gauche for hair and nail and gauche–gauche–trans for stratum corneum [293]. The latter is less stable. The altered geometry of disulfide bonds and the extreme folding of protein molecules in hair and nail result in a different degree of hydration. The looser structure of skin allows more free water, whereas the structure of hair and nail allows very little. This contrasting degree of hydration means that skin is capable of sustaining metabolic processes not seen in nail [293]. Keratins and the associated proteins fall into the following categories:

- low-sulfur proteins (40–60 kDa)
- high-sulfur proteins (10–25 kDa)
- high-glycine/tyrosine proteins (6–9 kDa).

It is believed that the low-sulfur keratins form 10 nm filaments and the latter two groups of proteins form an interfilamentous matrix. The diversity of keratins within humans and between different species lies in the permutations of these three proteins [296] and the diversity of the keratins themselves. Over 30 high-sulfur proteins have been identified in human nail by polyacrylamide gel electrophoresis [297].

Nail plate keratin fibrils appear orientated in a plane parallel to the surface and in the transverse axis [298]. They fall roughly into an 80 : 20 split between “hard” hair type (trichocyte) keratin and “soft” epithelial keratin [122]. These two variants are similar in many respects and share an X-ray diffraction pattern of α-helices in a coiled conformation, also confirmed using Raman spectroscopy [295]. Hard keratins split into the classic association of acidic and basic pairs, with extensive amino acid homologies with the epithelial forms [299]. In spite of regions of homology, the “hard” and “soft” keratins are distinguishable by immunohistochemistry [14, 16, 122]. The relative resilience of the two groups of keratins is also reflected by their solubility in 2-mercaptoethanol. At 50 mmol/L concentrations, only epithelial “soft” keratins are extracted from nail clippings. The concentration needs to be raised to 200 mmol/L before significant quantities of “hard” keratin dissolve [300].

The main lipid of nail is cholesterol. The total fat content is 0.1–1%, contrasting with the 10% found in the stratum corneum. The water content is less than that of skin, being 7–12% compared with 15–25%.

Biomarkers in nail

X-ray diffraction is one of the best tried methods of elemental nail analysis. Much of the initial work was done by Forslind [298], who observed that the hardness of the nail plate is unlikely to be due to calcium, which the analogy with bone has suggested. Detailed resumés of normal nail mineral content have been made [301].

Much interest has been demonstrated in the analysis of nails as a source of information concerning health. A significant increase in the nail content of Na, Mg, and P was noted in a survey of 50 patients with cirrhosis [302], and levels of ethyl glucuronide can be used as a marker in hair and nail for long-term high alcohol consumption. It is a minor metabolite of alcohol and can be detected in blood 24 h after 4 units of alcohol or up to 96 h after larger amounts. In nail it might act as a marker up to 12 weeks after ingestion and possibly longer [303]. In a comparison of term and preterm infants, a decrease in aluminum and sulfur was found in term deliveries. The high aluminum content in preterm infants was considered of possible relevance to the osteopenia observed in this group [19]. Copper and iron have been observed at higher levels in the nails of male 6–11 year olds in comparison with females [304]. This in turn has been reviewed in connection with autism and seen alongside increases of lead and other metals [305]. Iron levels in the general population were found to be equal in men and women, but higher in children and highest in the neonate [306].

In some respects, nail analysis can be compared with a blood test, but involving the examination of a less labile source of information. Analysis of chloride in nail clippings of a juvenile control population and those with cystic fibrosis revealed a significant increase of chloride, by a factor of 5, in the latter. This has led to the suggestion of “screening nail by mail” for inaccessible regions, where sending nails would be relatively easy.

The glycosylated globin molecule, used for estimation of long-term diabetic control, has been used as a
model in studies measuring nail furosine in diabetes mellitus. The nail fructose-lysine content is raised in this disease and has shown a correlation with the severity of diabetic retinopathy and neuropathy [307–309]. Nail furosine levels have also shown a good correlation with fasting glucose and may even compete with glycosylated hemoglobin as an indicator of long-term diabetic control [310].

Steroid sulfatase and its substrate, cholesterol sulfate, have been assayed in the nails of children being screened for X-linked ichthyosis and found to have adequate sensitivity and accuracy to be useful [303, 311, 312]. Sudan IV-positive material in nails has been measured as a guide to serum triglycerides [313].

Selenium is a trace element critical for the activity of glutathione peroxidase, which may protect DNA and other cellular molecules against oxidative damage. High concentrations are seen to protect against the action of certain carcinogens in some animal models, and consequently its role in human cancers has been explored. Analysis of the selenium levels of different rat tissues suggests that blood selenium may be the best indirect measure of liver selenium while nail selenium may best reflect whole-body levels and the level in skeletal and heart muscle [314]. Nail selenium levels in those being screened for oral cancer [315] and carcinoma of the breast [303, 316] showed no significant differences between affected and control patients. However, in a prospective study, toenail selenium levels had a weak predictive value for the development of advanced prostate cancer, where low levels of selenium predisposed to this malignancy [317]. Examination of a wide range of trace elements in the nails of women with breast cancer failed to show any difference from normal controls [318], and analysis of nail for zinc showed no significant difference between pellagra patients with low serum zinc and normal controls [319].

Nail represents a stable, cheap, and easily obtained source of DNA for a range of purposes including epidemiological studies [320]. After amplification by the polymerase chain reaction 5 mg is adequate, where good quality nail can be obtained from cadavers more than 6 months after death yielding DNA adequate for forensic identification [321].

**Exogenous materials in nail analysis**

Exogenous materials can be considered in two groups: environmental and ingested substances. In the first category, cadmium, copper, lead, and zinc were examined in the hair and nails of young children [322]. This was done to gauge the exposure to these substances sustained in rural and industrialized areas of Germany. Both hair and nail reflected the different environments, although the multiple correlation coefficient was higher for hair than for nails. Similar work with lead and cadmium in 200 Kenyan children demonstrated that the level of heavy metals in their fingernails correlated more to the location of their school than to their home [323]. Where comparable studies are done with adult disease and control groups, it has been shown that those with coronary heart disease and hypertension have significantly higher levels of chromium and zinc and lower iron than healthy matched controls [324]. It remains difficult to lend a clear interpretation to these results in terms of their biological significance and whether they are observations of cause or effect.

Water taken from wells in arsenic-rich rock has resulted in arsenic poisoning on a major scale in West Bengal, India, over the last 10 years. About 50% of ingested arsenic is excreted in the urine, with smaller amounts in the feces, hair, and nails. Nail analysis has been used in the Bengal population as well as in other populations with arsenic poisoning. Levels were estimated using flow injection hydride generation atomic absorption spectroscopy, which allows analysis using very small samples and enables comparisons between different tissues. The Bengal experience suggests that there are similar concentrations in hair and nail, with a trend towards higher concentrations in the latter [325]. During an episode of arsenic poisoning in Alaska, USA, the level of arsenic in nail was four times that found in hair [326]. A study in New Hampshire, USA, found that, in subjects drinking from arsenic-rich wells, there was a doubling of toenail arsenic for a 10-fold rise in water arsenic content [327].

The features of arsenic poisoning were different in Alaska and Bengal, with far more cutaneous and systemic signs of toxicity in the Bengali population in spite of similar levels in body tissues. This was attributed to coexistent dietary deficiencies and ill-health in the Bengalis. In affluent North American communities, higher toenail arsenic has been associated with prolongation of the QT interval on electrocardiograph [328]. This could be due to an effect on the flux of calcium currents in cardiac cell membranes and clinically could contribute to disease. Risk of coronary heart disease is found to be correlated with nicotine concentration in toenail samples as revealed in a substantial cohort followed between 1984 and 1998 [329].

In many countries fluoride is added to drinking water as a public health measure. In forensic terms, it can be a means of identifying whether the person originated from a fluorinated district or not, where hair, nail, and teeth can all be measured for fluoride content to reveal exposures of different temporal profile [275].

Nickel analysis has been performed to establish occupational exposure [330].

The use of forensic nail drug analysis has been reported by the Japanese, where over 20 000 people were arrested for the abuse of metamfetamine in 1987 [331, 332]. It was
found that the drug entered the nail via both the matrix and nail bed. Chronic drug abusers could be distinguished from those with a single recent ingestion by scraping the undersurface of the nail before analysis. This would remove the nail bed contribution and the drug it contained in the “one-off” abuser.

Simultaneous hair and nail analysis has been performed to compare the capacity of the tissues to reflect chronic drug abuse in those taking cocaine [333] and amphetamines [334]. Miller et al. [333] found that concentrations of cocaine and its derivatives were higher in hair than in nail, whereas Cirimele et al. [334] found that the concentrations of amphetamines and their metabolites were similar in both tissues. Analysis of nail clippings from the newborn by gas chromatography–mass spectroscopy can provide evidence of exposure to cocaine during embryogenesis. Given the point of nail formation, it is likely that the levels will reflect exposure after the 14th week [335]. Inclusion of the antifungal terbinafine via the nail bed has also been observed [336]. Access of the drug to the nail plate via the nail bed may be one of the important factors allowing effective therapy to be delivered in less time than it takes to grow a nail [337, 338]. In vitro models for the uptake and delivery of terbinafine by nail plate have been employed to examine aspects of this process [339].

Following single large doses of metamfetamine, it can be detected by mass fragmentography in saliva up to 2 days later, hair up to 18 days, and in nail for the next 45 days [332]. Chloroquine [340] has also been measured in nail clippings for research purposes up to a year after ingestion.

Electron paramagnetic resonance is a laboratory tool for the measurement of a stable radiation-induced signal yielded by nail keratin. This signal reflects personal radiation exposure and can be detected on nail clippings. The method is used for individuals or on multiple samples for assessment of population exposure [341]. The advantages over the earlier technique of undertaking a bone biopsy are substantial [295]. Thermoluminescence and optically stimulated luminescence are also candidate techniques for measuring radiation signals from  α-keratin [294].

Physical properties of nails

Strength

The strength and physical character of the nail plate are attributable to both its constituents and design. The complex pleated and cross-linked keratin mesh provides the basis for a strong structure. The cross-linking reduces the water content within the molecule and potential for water solubility or active hydration. In addition there is a theory that proposes that keratin molecules and the intervening matrix are locked into the dehydrated state through oxidation and “curing.” This results in a semi-rigid structure that does not alter its properties to any significant degree when immersed in water [342]. The features of geometric design worthy of note are the double curvature, in transverse and longitudinal axes, and the flexibility of the ventral plate compared with the dorsal aspect. The first provides rigidity, whereas the latter allows moderate flexion deformity and slightly less extension. The most proximal component of the matrix provides the corneocytes of the dorsal nail surface. These usually provide a shiny surface. When the matrix is altered by disease or the nail surface subject to trauma, this shine is lost.

Measuring nail strength

Several techniques have been developed to study the physical properties of nails [343–345]. Maloney and Paquette’s study [344] showed changes of tensile, flexural, and tearing strength with age, sex, and the digit from which the nail derived. Finlay et al. [345] devised a “nail flexometer” able to repeatedly flex longitudinal nail sections through 90°, recording the number it took to fracture the nail. In this way, the strength could be quantified. He noted that the immersion of nails in water for 1h increased their weight by 21%. It also made them significantly more flexible. After 2h, the flexibility was still increasing, whereas the water content reached a plateau. Analysis of in vivo nail by Raman spectroscopy suggests that, after soaking in water for 10 min, the  α-helical protein conformation is made more loose, with greater spacing between proteins as water occupies the interstices. However, this change is seen only in distal nail, with proximal nail already manifesting a high degree of hydration before immersion [346]. Farren et al. [159] has used simple cutting tests, measuring the force needed to cut nail plate with scissors. They noted that it takes 50% more force to cut a nail longitudinally than transversely and attributed this to the trilaminar structure of nail with orientation of keratin fibrils that favors longitudinal over transverse strength.

Mineral oil has no effect on flexibility, although it can act to maintain some of the flexibility imbued by water. This principle is applied in the treatment of onychoschizia, where repeated hydration and drying of the nail plate results in splitting at the free edge [184]. Zaun [347] has used a method of assessment of brittleness that relies on the swelling properties of nail, employing the technique before and after therapy for brittle nails. Splitting can be partially overcome by applications of emollient after soaking the nails in water. The use of nail varnish can also decrease water loss [348].
Permeability

Nail permeability is relevant to topical drugs on the dorsal surface and systemic drugs from the ventral surface. It can be measured using a range of techniques, including near-infrared Fourier transform Raman spectroscopy, near-infrared diffuse reflectance Raman, attenuated total reflectance Fourier transform infrared, dynamic vapor sorption near-infrared, confocal Raman spectroscopy, atomic absorption spectrometry, gamma ray spectrometry, energy dispersive X-ray spectroscopy, dielectric spectroscopy, opto-thermal transient emission radiometry, optical coherence tomography, confocal laser scanning microscopy, and transonychial water loss (TOWL) [349]. The principal characteristic of nail with respect to drug penetration is that it behaves more like a hydrophilic gel membrane than a lipophilic membrane such as the stratum corneum. TOWL can be measured in vivo [350] but drug penetration assay is more complicated. The simplest method is to use cadaver nails. Doing this, the permeability coefficient for water has been estimated at $16.5 \times 10^3$ cm/h and that for ethanol at $5.8 \times 10^5$ cm/h [351]. This demonstrates that the hydrated nail is more permeable to water than to alcohol and behaves like a hydrogel of high ionic strength to polar and semipolar alcohols. Looking at nail permeability in states of different relative humidity demonstrates that diffusivity of nail increases logarithmically, with an overall increase of 400 times from dryness to complete hydration [352]. Combining alcohols with water may increase the permeation by the alcohol. The addition of $N$-acetyl-L-cysteine or mercaptopetoethanol to an aqueous solvent has been found to enhance the penetration of nail samples by the antifungal tolnaftate [353]. Human nail can be substituted in such studies using an in vitro model for the assessment of drug penetration employing a keratin membrane prepared from bovine [354], sheep [355], and porcine hooves [356, 357].

The nail is 1000 times more permeable to water than is skin [358, 359] and, consequently, drugs required to diffuse through the nail should normally have a high degree of water solubility [360]. In spite of this, there is possibly a parallel lipid pathway that allows permeation of hydrophobic molecules [361] and lipid vehicles are of value because they stick better to the nail surface [354, 360]. Molecular size, expressed as weight, is a further factor determining the penetration of nail by a drug. Larger molecules penetrate less well. In the field of topical antifungals, this allows prediction of efficacy when the combined characteristics of water solubility, molecular size, and minimum inhibitory concentration for antifungal activity are allowed for in a complex calculation [362]. In this manner, drugs such as ciclopirox and amorolfine can be predicted to be of some value. However, more hydrophobic molecules, such as the imidazoles, itraconazole, and ketoconazole, are barely able to diffuse into nail, even when it is pretreated with topical keratolytics such as papain, urea, and salicylic acid [363]. The main pharmacological sphere of attempting nail penetration by drug is for the treatment of fungal nail disease. It is of note that in vitro work with normal and onychomycotic nails showed little difference in nail drug penetration between the two [364].

The dense matrix of keratin and associated proteins is considered an obstacle to dimethyl sulfoxide (DMSO) penetration in the nail plate, contrasting with its easier access through skin [361]. Keratin affinity influences the rate of penetration such that a molecule that has high affinity has limited flux, whereas a molecule that is otherwise similar, but that has low affinity, is able to pass through the nail more easily [365]. This can in turn enhance clinical efficacy [366]. However, in spite of the molecular incompatibilities, DMSO can facilitate the penetration of some topical antifungals [367]. When amorolfine is applied to nail, its penetration is enhanced by pretreatment with DMSO and the penetration is further enhanced if methylene chloride is used as a vehicle for the antifungal in preference to ethanol [368]. Onychomycosis itself may increase penetration of the nail by an applied product [369]. With fungal infection, tensile strength reduces. Porosity to water remains unchanged but porosity to rhodamine and ethanol increases at the same time as the nail thickens. Raman spectroscopy suggests that the S–S bonds are retained although there was a differential in the peak emission suggesting that the ventral nail surface is altered and the dorsal surface unchanged. This would fit with the common pattern of fungal invasion gaining nail plate access through the ventral aspect [370]. Some medicated lacquers are also able to penetrate sufficiently to be of clinical use, particularly if their access is increased by abrading the dorsal surface of the nail plate [371, 372]. The concentration gradient, and hence diffusion, can be increased further by facilitating solution of the reagents, such as miconazole, by lowering the pH [373]. Using a solvent that evaporates will have the same effect [374].

Iontophoresis of chemical across a concentration gradient of drug of 50–100 mm has also been attempted with some success [375–378]. The problem mainly related to the practicality of the process and flux of sodium, potassium, chloride, and water (TOWL) through the nail under iontophoretic influence in comparison with normal passive flow [379]. The pathway can be via the proximal nail fold if matrix is the target [380]. With formulations of low surface tension, the film may travel around the free edge of the nail into the subungual space – particularly relevant to early infections of distal nail [377].

Recent studies with common antifungal agents have been encouraging [381, 382], where changing pH [383,
employing penetration enhancers such as DMSO [385], mannitol [386], low-molecular-weight polyethylene glycols [387], ascorbic acid, and acetylcysteine [388] improves drug penetration. Acetyl cysteine is known to disrupt nail structure, which can be evaluated with infrared and impedance spectroscopy [389]. The longer term significance of such disruption is not clear. The clinical relevance of the level of penetration relies on movement of drug across two boundaries. First, drug entry into the nail needs to be enhanced in order to be effective within the nail. However, possibly even more important is the further stage of the drug leaving the nail and entering the subungual tissues to kill fungus at this sequestered site. The subungual tissues are very variable in their apposition to the nail and in their character. There may be onycholysis, with no contact between nail and nail bed, thick keratin between the two, or a layer of loosely compacted material and squames with secondary bacterial or yeast infection. Although the rate of drug flow from nail into an in vitro chamber can be measured [390], it is not the same as demonstrating a clinical effect in the heterogeneous settings that prevail with onychomycosis. New drug molecules suited to nail penetration provide scope for topical therapy to improve [391–393].

There is also exchange of chemicals between nail and the internal environment, and it is likely that the nail has different characteristics of drug penetration on the dorsal and ventral surfaces [394]. The significance of this is mainly with respect to inclusion of circulating materials into the nail rather than the other way around, although in a study of topical application of sodium pyrithione Mayer et al. [395] found microscopic amounts in the systemic circulation. Munro and Shuster [338] and Matthieu et al. [337] have shown that drugs can penetrate rapidly into the distal nail via the nail bed. Other drugs may be found in the nail, which makes the nail a useful source of information concerning the ingestion of some illicit drugs or environmental pollutants (Table 1.9).

Nail has been compared with other keratinous tissues, such as hair, hoof, and skin, to determine how well it provides a model of in vitro infection by fungi [396]. This reveals that nail is relatively resistant to such infection and hair, feathers, and horn were more easily penetrated.

Radiation penetration

The permeability of the nail plate to radiation has both advantages and drawbacks. It is the basis for treating 20-nail dystrophy with topical photochemotherapy [397] and also the cause of photoonycholysis. This may be in association with photosensitizing drugs [398]. Benign longitudinal melanonychia can complicate phototherapy for psoriasis [399].

Chronic X-irradiation is associated with carcinoma in situ and invasive squamous cell carcinoma [400]. The polydactyly form of Bowen disease is historically related to some source of radiation [401]. Parker and Diffey [402] have investigated the transmission of light through the toenails of cadavers. Examining wavelengths between 300 and 600 nm, it appears that transmission at the shorter wavelength is minimal. This corresponds to ultraviolet B (UVB). If the nail plate is acting as a sunscreen it is fortuitous, but the character of the toenails studied may not be the same as fingernails, which are more commonly exposed. Exposure of trichophyton rubrum cultures to UVA, UVB, and UVC demonstrates effects at all three wavelengths. However, only UVB and UVC reduced colony size. In principle this might illustrate an opportunity to treat onychomycosis with ultraviolet radiation, but the dosimetry and penetration were not established in this study. It remains possible that ultraviolet provides some level of inhibition of onychomycosis on fingernails, contrasting with toenails with their differential natural light exposure.

Debate surrounds the possible risk of squamous cell carcinoma arising in the nail unit or nearby skin due to ultraviolet irradiation arising from ultraviolet curing used in acrylic nail practices. The original work suggests that, although UVA penetrates nail, it is not at sufficient doses to cause harm to the nail unit or nearby [403, 404]. Subsequent reports [405] suggest otherwise. This is questioned on technical grounds by Dowdy et al. [406] on the basis that the wrong radiation meter was used in the assessment of dosage delivered by the nail-curing equipment. All this work had been done on single radiation sources whereas a study undertaken on 17 sets of equipment used in nail salons attempted to determine what variation there was in normal use. This demonstrated substantial differences between ultraviolet lamps and also between points in the field irradiated by each lamp. However, the overall doses remained small and the authors concluded that the risk to clients was also small and could be avoided on the normal skin by wearing gloves with finger tips open [407].

A double-blind study of superficial radiotherapy in psoriatic nail dystrophy has demonstrated a definite, albeit temporary, benefit [408]. A similar temporary benefit has been demonstrated with electron beam therapy [409]. Both of these studies might suggest that the different forms of radiation are penetrating nail, although treatment of periungual psoriasis can have a secondary beneficial effect on subungual tissues.

The nail is also permeable to electric direct current, which has been examined in dry and hydrated settings in vitro and in vivo. The passage of current with a voltage of 0.5–9 V does not cause any physical alteration to the nail and provides a baseline for the delivery of medication using iontophoresis. At higher voltages there is a perception by the patient when in vivo [410], and in the setting of phosphate buffer hydration the nail resistance can drop after 2 h.
References


102 Langner I, Krüger PC, Evert K et al. (2013). MR microscopy of the human finger and correlation with...


301 Zaia especial. The Nail in Health and Disease, 2e. Norwalk, CT: Appleton and Lange.


423 Kreuter A, Gambichler T, Pfister H et al. (2009). Diversity of human papillomavirus types in


Chapter 2

Physical Signs

Adam Rubin1, Mark Holzberg2, and Robert Baran3

1 Departments of Dermatology, Pediatrics, and Pathology and Laboratory Medicine, Hospital of the University of Pennsylvania; Children’s Hospital of Philadelphia, Perelman School of Medicine at the University of Pennsylvania, Philadelphia, PA, USA
2 Department of Dermatology, Emory University School of Medicine, Atlanta, GA, USA
3 Hon. Pr. of the University of Franche-Comté; Nail Disease Centre, Cannes, France

Modification in the configuration of the nail unit

Clubbing or Hippocratic fingers

Clubbed fingers have been known since the first century BC, when Hippocrates first described the sign in patients with empyema. The morphological changes combine: (i) increased transverse and longitudinal curvature of the nails and (ii) enlargement of the soft tissue structures, strictly confined to the fingertips [1]. The increased nail curvature is most prominent in the radial three digits. The curvature is variable; the deformity may be fusiform, shaped like a bird’s beak, and clubbed, resembling a watch glass. Associated cyanosis is fickle. These shape types can be found in all of the four main forms of clubbing (Figs 2.1–2.4). For a more complete discussion of clubbing, see Chapter 15 and the Appendix.

Koilonychia

Koilonychia is the converse of clubbing, the nail being concave with the edges everted, the so-called “spoon nail.” This dystrophy, which becomes more apparent when the nail is viewed laterally, normally affects several fingers, especially the thumb. All the fingers may be involved and, less frequently, the toes. The exception is in the first few years of life when it is a common normal finding in the great toes. The underlying tissues may be healthy or affected by subungual hyperkeratosis, which
is clearly visible at the margin. This would suggest psoriasis, or an occupational origin of the deformity; the first three digits are frequently involved in the latter case. The nail, which may be normal, thinned, or thickened and sometimes soft, has a smooth surface when the koilonychia is idiopathic. Longitudinal splitting with koilonychia in each of the separated parts of the nail plate

Figure 2.1  Clubbing. Lovibond’s “profile” sign: the angle is normally less than 160° but exceeds 180° in clubbing.

Figure 2.2  Clubbing. Curth’s modified profile sign.

Figure 2.3  Clubbing. Schamroth’s sign. The “window” is lost in clubbing, with a prominent distal angle between the ends of the nail.

Figure 2.4  (a) Clubbing in pachydermoperiostosis. Courtesy of P.Y. Venencie. (b) Pachydermoperiostosis, severe skin changes.
appears in some cases of lichen striatus, and in certain inherited conditions [2]. Some or all of the fingernails may, in contrast, present with a central, longitudinal ridge in place of the fissure. In the trichoonychotic hidrotic ectodermal dysplasias, for example, there is a peculiar longitudinal fold increasing distally. This divides the nail plate with separated koilonychia on each side and without abnormalities elsewhere (Figs 2.5, 2.6).

The “serrated koilonychia” syndrome [3] combines spoon nail and transverse grooves involving all the digits; steroid injections in the proximal nail fold lead to a temporary improvement.

The petaloid nail is a variant of an early stage of koilonychia, in which flattening of the nail is the characteristic sign. A variety of koilonychia is the type known as "ongle en fermoir d’épingle de nourrice," in which the deformity is shaped like the catch on a safety pin.

Koilonychia may be induced by a variety of factors, including reduction in blood flow, localized skin diseases affecting the nail unit, endocrinopathies, nutritional deficiencies, as well as capillary shunt influences. Common nail disorders such as lichen planus, psoriasis, and trachyonychia may demonstrate koilonychia as part of the disease process [4]. See also the Appendix.

Transverse overcurvature of the nail

There are three main forms of overcurvature (Fig. 2.7): arched, pincer, trumpet or omega nail; tile-shaped nail; and “plicated” nail.

Pincer nail (see also Chapter 22) is a dystrophy characterized by transverse overcurvature that increases along the longitudinal axis of the nail and reaches its greatest proportion at the distal part. At this point, the lateral borders tighten around the soft tissues, which are pinched without necessarily breaking through the epidermis (Fig. 2.8). In extreme cases, they may join together, forming a tunnel, or they may roll about themselves taking the form of a cone. In certain varieties, the nails are shaped like claws, sometimes resembling pachyonychia congenita. After a while, the soft tissue may actually disappear, and this may be accompanied by a resorption of the underlying bone [5] (shell nail syndrome).

Pincer nail is probably due to selective widening of the proximal region of the lateral matrix horns by juxtaaar-

![Figure 2.5 Koilonychia.](image)

![Figure 2.6 Koilonychia in trichoonychotic hidrotic ectodermal dysplasia.](image)

![Figure 2.7 Transverse overcurvature showing the three subtypes.](image)

(a) Pincer or trumpet nail; (b) file-shaped nail; (c) plicated nail with sharply angled lateral margins.

![Figure 2.8 Pincer nail deformity.](image)
ticular osteophytes. As the shape of the distal matrix does not change the nail plate assumes a conical shape which rises above the nail bed. As the nail is tightly bound to the periosteum, it lifts a traction osteophyte from the dorsum of the underlying phalanx [6].

This morphological abnormality would be no more than a curiosity if the constriction were not occasionally accompanied by pain which is sometimes provoked by the lightest of touch, for example the weight of a bedsheet in trumpet nails [7]. The origin of this dystrophy probably resides in a developmental anomaly and may be an inherited disorder [8]. Some cases have been attributed to the wearing of ill-fitting shoes. Underlying pathology, such as subungual exostosis in the toes and inflammatory osteoarthritis, should always be looked for, especially where the fingers are involved. Higashi [9] reported on six patients with pincer nail due to tinea unguium. The deformity resolved with oral griseofulvin. Reversible pincer nails after treatment with a beta-blocker is a rare etiology [10]. Pincer nails as markers of gastrointestinal malignancy are exceptional [11]. Pincer nails have been associated with systemic lupus erythematosus [12], arteriovenous fistula creation [13], and amyotrophic lateral sclerosis [14].

Recent surgical advances in the treatment of pincer nails include the use of a modified double Z-plasty [15], as well as a dermal flap [16].

The tile-shaped nail presents with an increase in the transverse curvature; the lateral edges of the nail remain parallel.

In the plicated variety of overcurvature the surface of the nail plate is almost flat, while one or both lateral margins are sharply angled forming vertical sides which are parallel (Fig. 2.9).

Although these deformities may be associated with ingrowing nails, inflammatory edema due to the constriction of the soft tissue is unusual. For treatment of these forms of nail overcurvature, see Chapter 22.

In terms of etiology and pathogenesis, three different types of transverse overcurvature have to be differentiated.

1) A symmetrical form, often hereditary and seen in several generations of a family and in several family members of the same generation; it is usually seen in toenails with both the great and the lesser nails being affected. It is usually associated with a malalignment of the nail’s long axis. The great toenail is deviated laterally, the other nails medially. Radiographic films show that the distal phalanx of the great toe also shows a slight lateral deviation, the base of the last phalanx is very wide and exhibits bony outgrowths pointing distally, and there is a small traction osteophyte on the dorsal tuft of the tip of the distal phalanx. Its histological examination reveals amorphous dense osseous material.

From proximal to distal, the nail bed epithelium becomes progressively more acanthotic, papillomatous, and hyperkeratotic with a marked hypergranulosis and round to oval globules of inspissated serous exudate in the subungual horn. There is also a marked dilatation of some capillaries in the tip of the nail bed’s papillary dermis.

2) An asymmetrical form that is acquired and may be due to trauma, surgery, or some dermatoses and is particularly associated with degenerative osteoarthritis of the distal interphalangeal joints of the fingers or foot deformation. This type is more frequently seen in elderly women. Radiography of the great toe also reveals a wide base of the distal phalanx with lateral and medial exostoses and sometimes also irregular subperiosteal bone appositions on the processus unguicularis and a small osteophyte on the dorsal aspect of the tip of the distal phalanx. Since the matrix is intimately and firmly attached to the bone its physiological curvature is unbent, which in turn leads to a less curved nail proximally but increasing its curvature distally. This heaps up the nail plate and induces a distal dorsal traction osteophyte. Treatment is aimed at releasing the outward pressure on the matrix by selectively removing the lateral matrix horns, and at spreading the nail bed [17].

3) Repeated nail avulsions, injury to the distal phalanx and the nail organ, as well as some dermatoses, particularly psoriasis and total dystrophic onychomycosis with secondary shrinking of the nail field, may cause transverse overcurvature of the involved nail.

**Dolichonychia**

Normally the quotient between the length and the width is 1 ± 0.1. In dolichonychia this quotient is greater: 1.9 [18]. Therefore the nails appear long and narrow. This condition may be seen in Ehlers–Danlos syndrome, Marfan...
syndrome, and hypohidrotic ectodermal dysplasia, in association with eunuchoidism or with hypopituitarism.

Brachyonychia/short nails/racket nails

(See acroosteolysis in Chapter 14 and the Appendix.) In this condition, considered in the past as a minor sign of congenital syphilis [19], the width of the nail plate (and the nail bed) is greater than the length (Fig. 2.10a–c), which is in contrast to the normal ratio of the length to the shape. It may occur in isolation or associated with a shortening of the terminal phalanx [20].

The “racket thumb” is usually inherited as an autosomal dominant trait. Ronchese [21] performed a review of 113 cases of racket thumbnail and found a sex ratio of three females to one male and a higher prevalence of bilateral cases. All the fingers may be involved. The epiphyses of the terminal phalanx of the thumb are normally closing at the age of 13–14 years in girls and slightly later in boys. In individuals with the hereditary defect the epiphyseal line is obliterated on the affected side at the age of 7–10 years, while it is still present according to age in the normal thumb. Among the 31 patients with racket nails studied by Higashi [22], two women presented only great toenail involvement.

A hallmark of the Rubinstein–Taybi syndrome, an autosomal dominant genodermatosis is the presence of broad thumbs and great toes. These patients also have growth and mental retardation, and multiple facial abnormalities. Rubinstein–Taybi syndrome is associated with mutations in the CREBBP and EP300 genes [23].

Racket nails have been reported in association with brachydactyly and multiple malignant Spiegler tumors [24]. Disorders associated with brachyonychia include cartilage–hair hypoplasia, acroosteolysis, Larsen syndrome, pyknody sostosis, and acrodysostosis. This condition may also be acquired in bitten nail, or associated with bone resorption in hyperparathyroidism [25, 26], psoriatic arthropathy, systemic sclerosis [27], as well as with acroosteolysis [28].

A thickened and large cuticle extending on the nail may mimic brachyonychia. The appearance of a racket

Figure 2.10 Brachyonychia. (a) Unilateral right thumb (left of image). (b) Radiograph of (a) showing the shortened terminal phalanx (left of image). (c) Clubbing associated with racket nails.
thumb nail may be improved through cosmetic surgery, narrowing the nail plate and creating lateral nail folds. This is accomplished by performing lateral–longitudinal nail excisions on both sides of the thumbnail (as is done with a lateral longitudinal biopsy) involving the matrix. Lateral nail folds are created after back-stitching is performed on the lateral soft aspects of the distal phalanx which have been dissected from the bone [29].

**Parrot beak nails**

This peculiar, symmetrical overcurvature of the free margin of some fingernails simulates the beak of a parrot [30] (Fig. 2.11a,b). If the patient trims the affected nails close to the line of separation from the nail bed, no abnormality would be noted clinically. Soaking the nails in tepid water for about 30 min causes this overcurvature to disappear temporarily. Distal hemitorsion of the nail plate observed in porphyria cutanea tarda [31] could be clinically related to the parrot beak nail. Parrot beak nails can be seen after fingertip injuries, because of bone loss, loss of nail bed support, and scar contracture. It can also be caused by tight closure of a fingertip amputation. Pandya and Giele [32] described a method of preventing the parrot beak nail in fingertip amputations by using a hypodermic needle to secure a flap and relieve tension at the leading edge of the flap at the hyponychium.

Payne-James et al. [33] described a new syndrome related to chronic crack-cocaine use that includes the triad of perniosis, finger pulp atrophy of the distal digits, and parrot beaked clawing of the nails. They documented eight women with these changes who were examined while in police custody. The thumbs and index fingers were most commonly affected. Some of the nails also had loss of the cuticle. These individuals were crack-dependent drug users, and not occasional or recreational users. Payne-James et al. postulates that prolonged cocaine-induced vasoconstriction causes a relative hypoxia in the digits, resulting in pulp atrophy, and curvature and hyperplasia of fingernails as a secondary phenomenon. Parrot beak nails can occur as a primary nail dermatosis, or secondary to finger pulp atrophy. Parrot beak nails can cause functional difficulties with the nails. The simplest treatment is to keep the nails clipped short [34].

![Figure 2.11](image_url) Parrot beak nail: different degrees between (a) and (b). (c) Curved nail of the fourth toe. (d) Circumferential nail. Courtesy of A. Griffiths.
Curved nail of the fourth toe (Fig. 2.11c)

The common feature of this congenital condition is a curved fourth toenail, often bilateral. Eight cases were reported by Higashi et al. [35] without other anomalies of the extremities. Additional hypoplasia of the bone and soft tissue was present in the cases reported by Iwasawa et al. [36]. This nail deformity resembles a post-traumatic fingertip abnormality, in which the loss of the supporting tissues for the nail leads to curving of the nail. With congenital curved nail of the fourth toe, the primary defect is congenital shortening of the distal phalanx, and the curved nail plate is a secondary phenomenon. It is not clear whether the series of Iwasawa et al. [36] described the same pathology as that of Egawa [37] or Miura [38], in which the deformities of the nails in these series resembled those in that of Iwasawa et al.

Another curved nail anomaly is Kirner’s deformity, but this is usually absent before 12 years of age [39]. Congenital curved nail of the fourth toe is inherited as an autosomal recessive trait. Lin et al. [40] described three Taiwanese patients with congenital curved nail of the fourth toe that demonstrated fusion of the distal and middle phalanges of the affected digits. There was bony hypoplasia of the fourth toe of these patients. Curved nail of the fourth toe is usually asymptomatic. Kang et al.’s [41] patient, who was 7 years old, presented bilateral fourth toenails covering not only the dorsal but also some of the plantar aspect of the distal phalanx.

Circumferential fingernail (see Chapter 9) (Fig. 2.11d)

Alves et al. [42] described a tubular nail plate resembling a punch biopsy involving the left ring finger of a 7-year-old Brazilian girl. This extremely rare congenital malformation was associated with other bony and soft tissue abnormalities of the affected limb. Another case of circumferential fingernail was described in a 4-month-old boy that demonstrated a totally circumferential nail on the left small finger. This child’s upper extremities were slightly shortened. The abnormal fingernail was described as growing around the sides and on the palmar and dorsal surfaces of the terminal pulp. This finger was fixed in an extended position, was markedly tapered, and demonstrated clinodactyly. This patient had many other congenital anomalies. The original patient reported to have a circumferential fingernail was noted to have this finding at 7 months old. He had a documented chromosome 6 abnormality, and had multiple congenital anomalies. The volar surfaces of the ulnar half of the palms and small fingers were noted to be covered with dorsal skin. There were well-formed nails on both the dorsal and palmar surfaces of the small fingers. There was clinodactyly of the ring and small fingers, which were markedly tapered [43].

Claw-like nail

One or both little toenails are often rounded like a claw. This condition predominates in women wearing high heels and narrow shoes and is often associated with the development of hyperkeratosis such as calluses on the feet. Congenital claw-like fingernails and toenails have been reported [37]. Claw nails may be curved dorsally showing a concave upper surface.

Macronychia and micronychia

The nails are larger or smaller than normal and affect one or more digits with wide or narrow nail bed areas and matrices. They may occur as an isolated defect or in association with megadactyly, as in von Recklinghausen disease, or in epiloia. In fact macrodactyly may be the forme fruste of a wide variety of connective tissue abnormalities. It has been associated with the Proteus syndrome (partial gigantism, hemihypertrophy, etc.) [44] (Fig. 2.12), Maffucci syndrome, and Klippel–Trénaunay–Weber syndrome. Greenberg et al. [45] reported on a patient with epidermal nevus syndrome who also exhibited bilateral, four-finger megadactyly. Involvement of both hands and both feet of the same patient is unique [46].

Macroductyly most commonly manifests in the middle and index fingers [47]; usually corresponding to the territory supplied by the sensory branches of the median nerve, which was designated as nerve territory orientated macrodactyly or NTOM for short [48]. Finger incurvation may be neurological in origin [49]. Macroductyly associated with plexiform neurofibroma of the medial plantar nerve of the right foot is an unusual localization [50]. About one-third of neural fibrolipomas are associated with overgrowth of bone and macrodactyly [51, 52]. Distant benign lipoblastomatosis in the axilla has been reported [53]. As a rule, the involvement by macroductyly fibrolipomatosis is almost always unilateral.

Figure 2.12 Macronychia associated with megadactyly.
Pseudomegadactyly is an anecdotal presentation of chronic granulomatous paronychia resulting in hypertrophy of nail plate and bed [54].

Duplication of the distal phalanx is usually accompanied by a wide digit with a bivalved nail, fissured or confluent [55–57] (Fig. 2.13). Nail plasty with refinements, based on a lunula, focusing on constructing a good appearance of the nail in the treatment of duplicated thumb, has been advocated by Iwasawa and Hirose [58].

In Iso–Kikuchi syndrome, also known as congenital onychodysplasia of the index finger, or COIF syndrome (Chapter 9), the micronychia is usually medially sited instead of a centrally placed small nail, except for a less common type termed “rolled micronychia” [59] in which the nail is centrally located.

Apparent micronychia may be due to overlapping of the nail surface by thickened lateral nail folds. This is sometimes seen in Turner syndrome, in which the whole paronychium may be affected as in recalcitrant chronic paronychia [60]. Micronychia is often observed in Zimmerman–Laband syndrome [61]. Micronychia has also been observed with clubfoot [62]. Multiple isolated congenital micronychia has been treated successfully with nail bed expansion surgery [63].

Worn-down nails

Patients with atopic dermatitis or chronic erythroderma may be “chronic scratchers and rubbers.” The surface of the nail plate becomes glossy and shiny and the free edge is worn away. “Usure des ongles” may also occur in many different manual occupations [64] (Fig. 2.14a). This

---

**Figure 2.13** (a) Duplication of the nail. Courtesy of A. Tosti. (b) Duplication of the nail: diagram of associated bony changes: (i) bifid distal phalanx; (ii) duplicated distal phalanx.

---

**Figure 2.14** (a) Shiny, “worn down” nails. (b) Triangular defect involving the dominant hand in the “bidet nail.”
condition has been described as an occupational hazard of mushroom-pickers handling heavy, plastic bags [65]. A French variant of the worn-down nail syndrome, the “bidet nail,” has been reported by Baran and Moulin [66] (Fig. 2.14b). The dystrophy of the middle three fingernails of the dominant hand involved three unrelated women. The defect was triangular with its base lying at the free edge of the nail where the thinning was maximal. All three were fastidious females in whom the desire for cleanliness verged on the obsessional. All three were traumatizing their nails against the glazed earthenware of the bidet.

An 8-year-old girl was reported with the worn-down nail syndrome that affected all fingernails. The nail changes were caused by a habit of scratching her desk with her nails and fingertips [67]. Her nails demonstrated triangular thinning of the distal nail plate associated with pink erythema of the distal nail bed. Dermoscopic evaluation of the nails in this case demonstrated erythema of the nail bed with dilated capillaries and pinpoint hemorrhages in thinned areas.

Similar morphological findings to worn-down nails have been described in “lacquer nail”, which occurs after excessive use of a nail file by patients in caring for onychomycotic nails treated in association with topical nail lacquers [68]. With a similar pathogenesis, worn-down nails have also been described after acrylic nail removal [69] (see Chapter 19). Nail changes related to the worn-down nail syndrome do not permanently alter the nail unit.

**Onychatrophy**

Acquired (e.g. lichen planus, Chapter 14) and congenital onychatrophy present as a reduction in size and thickness of the nail plate, often accompanied by fragmentation and splitting. This condition may progressively worsen, with scar tissue eventually replacing the atrophic nail plate (Fig. 2.15).

**Anonychia** (see Chapter 14)

This implies absence of all or part of some or several nails (Fig. 2.16a,b). In aplastic anonychia, a rare congenital disorder occasionally associated with other defects such as ectrodactyly, the nail never forms [70–72]. Loose horny masses are produced by the metaplastic, squamous epithelium of the matrix and the nail bed in anonychia keratodes. Kelikian [48] states that “one cannot conceive of a normal nail above an anomalous ungual phalanx.” It would appear that congenital anonychia and hyponychia may be “bone territory”-dependent disorders [73]. The development of a normal nail is not only dependent on the underlying bone but this dependence may also extend to the middle phalanx. Anonychia or hyponychia may result when the underlying phalanx is either hypoplastic or completely absent (Fig. 2.17). Congenital forms have been reported as a part of different syndromes such as the
nail–patella syndrome, where hypoplasia of the nail plates is its hallmark. In the least affected cases only the ulnar half of each thumbnail is missing. Onychodystrophy–deafness and Cook syndrome are also affected by the nail anomaly (Chapter 9). A variety of genetic syndromes are associated with congenital anonychia, and often other areas of the body are affected outside of the nails. Recently, acquired anonychia has been described in cutaneous T-cell lymphoma [74].

In acquired nail atrophy (anonychia atrophica), the damage to the matrix can result in a rudimentary nail reduced to a corneal layer or to progressive scar formation; it is impossible to draw a strict line between anonychia and onychatrophy. In contrast to these permanent types, a transient anonychia can be due to a local or systemic condition, for example after retinoid therapy.

**Hypertrophy of the nail**

Hypertrophy may be acquired, as a result of dermatological or systemic conditions, including trauma, or occur as a developmental abnormality.

**Pachyonychia**

Pachyonychia is characterized by thickening of the nail. When the thickening is regular and confined to the nail plate, it is due to involvement of the matrix and is sometimes called *onychauxis*. This sign has been reported in association with the eunuchoid state.

Hyperplastic subungual tissues, especially of the hyperonychium, can alter the nail plate and nail consistency may be hard, as in pachyonychia congenita, or soft, as in psoriasis, pityriasis rubra pilaris, chronic eczema, and onychomycosis.

In pachyonychia congenita (Jadassohn–Lewandowsky syndrome) the nails are yellow-brown in color and extremely hard (Fig. 2.18). There is increased transverse overcurvature with a free edge shaped like a horseshoe or a barrel. All the nails may be affected but the toenails are less severely involved. Recurrent paronychia results in repeated shedding of the nails.

Histology shows a normal proximal nail fold and matrix. The nail plate is normal or moderately thickened, but its structure is normal. The nail bed shows marked acanthosis, papillomatosis, and huge hyperkeratosis. Groups of amorphous periodic acid–Schiff (PAS)-positive globules are arranged in vertical columns between the keratin masses of the subungual hyperkeratosis [75]; they are very similar to those seen in pincer nails and probably represent serum inclusions. Electron microscopy confirms the acanthosis and shows hypergranulosis representing serum inclusions. There is no difference between classical and late-onset pachyonychia congenita [76, 77].

**Onychogryphosis (onychogryposis)**

Onychogryphosis may rarely occur as a developmental abnormality but is usually acquired. It is most common in the toenail and presents as an uneven, thickened, opaque nail plate on a hyperplastic nail bed. The hallux is particularly vulnerable and the nail is often shaped like a ram’s horn and is brownish in color. Its irregular surface is marked by striations which are most frequently transverse. The matrix produces the nail plate at uneven rates; the faster growing side determines the direction of the deformity [60]. In the case reported by Ohata et al. [78], the free edge of the deformed nail plate reentered the proximal nail fold with subsequent granulation tissue and ulcer. Onychogryphosis is obvious when the changes are marked (Fig. 2.19a). In the early stages, however, when there is just a mild hypertrophy of the nail plate, diagnosis may present some difficulty.

In the elderly, the dystrophy is usually caused by pressure from footwear. The bend of the nail is medially directed, accentuated by hypertrophy of the nail bed.
Onychogryphosis may be related to weight-bearing function of the great toe, especially at the step-off phase. In cases when the free edge of the great toenail is considerably shorter than the tip of the great toe, the distal tissue bulge causes the onychogryphosis, which is due to primarily improper shorter nail cutting [79]. Therefore, for these authors, surgical treatment should be that of distal ingrowing nail.

Onychogryphosis, indicating longstanding poor personal care, appears in cases of self-neglect and is often seen in homeless persons and in senile dementia. Although this dystrophy may be a source of discomfort, or even pain when shoes are worn, it is usually accepted without complaint. In old age, fungal infection associated with onychogryphosis is not unusual [80]; it may be restricted to a single fingernail. Symptomatic onychogryphosis may be due to diseases such as ichthyosis and psoriasis (Fig. 2.20a). Pemphigus, syphilis, and variola [81] are exceptional causes. Nail resembling cutaneous horn may occur after acral bone loss [82].

Impairment of the peripheral circulation may produce onychogryphosis. Occasionally in the elderly, the pressure on the thickened onychogryphotic nail will initiate subungual gangrene [83]. Onychogryphosis may be considered as one of the manifestations of hyperuricemia [84].

Onychogryphosis may result from an injury to the matrix, scarring of the nail bed, and pathology in the central or peripheral nervous system (Fig. 2.19b). The traumatic type is common in young people.

In hereditary onychogryphosis [85, 86], all the nails of both hands and feet may be involved. The deformity is congenital and particularly marked during the first year of life. The disease is inherited as an autosomal dominant trait. Hemionychogryphosis may result from congenital malalignment of the great toenail and can be prevented by surgical correction of the deformity. One of the signs of the Iso–Kikuchi syndrome is hemionychogryphosis of

**Figure 2.19** (a) Onychogryphosis. (b) Onychogryphosis following peripheral nervous injury.

**Figure 2.20** Onychogryphosis due to psoriasis. (a) Dorsal aspect. (b) Ventral aspect.
the index finger (Chapter 9). Onychogryphosis is a feature of the Haim–Munk syndrome, an autosomal recessive genodermatosis caused by mutations in the cathepsin C gene, that produces a lysosomal protease. Other manifestations of this syndrome include palmo-plantar keratoderma, severe and early-onset periodontitis, pes planus, acroosteolysis, and arachnodactyly [87]. In infants and children, onychogryphosis can be associated with congenital malalignment of the great toenails [88].

Recently, in a series of 14 patients with onychogryphosis of the great toe, total matricectomy and V-Y advancement flap technique was employed for therapy. Patient satisfaction was rated as very good in nine patients and good in five patients [89].

**Modification of the nail surface**

**Longitudinal lines**

Longitudinal lines, or striations, may appear as indented grooves or projecting ridges.

**Longitudinal grooves**

Longitudinal grooves represent long-lasting abnormalities and can occur under the following conditions.

1) Physiological, as shallow and delicate furrows, usually parallel, and separated by low, projecting ridges. They become more prominent with age and in certain pathological states, such as lichen planus, rheumatoid arthritis, peripheral circulatory disorders, Darier disease, and other genetic anomalies.

2) Onychorrhexis is a series of narrow, longitudinal parallel furrows which have the appearance of having been scratched by an awl. Sometimes dust becomes ingrained in the nail surface. Splitting of the free edge is common.

3) Tumors located in the proximal nail fold area may exert pressure on the nail matrix and produce a wide, deep, longitudinal groove or canal, which will disappear if the cause is removed.

4) Median nail dystrophy. This uncommon condition consists of a longitudinal split of the thumbnails in the midline or just off center, starting at the cuticle and growing out of the free edge. It may be associated with an enlarged lunula [90]. In the cases described by Heller [91], the base of a 2–5-mm-wide groove with steep edges showed numerous transverse defects (Fig. 2.21). Often a few short feathery chevron-shaped cracks extend laterally from the split, a characteristic pattern, the inverted fir-tree. The so-called “naevus striatus symmetricus of the thumbs” [92] corresponds to this form [93]. Median nail dystrophy is usually symmetrical and most often affects the thumbs. Sometimes other fingers are involved, seldom the toes (usually the great toe). After several months or years, the nail returns to normal but recurrences are not exceptional. Sutton and Waisman [94] reported a “solenonychia” with a flabby filament of fleshy tissue present in the toenail canal. Familial cases have been recorded [95]. Drug-induced cases are very rare (isotretinoin, ritonavir). Usually the etiology is unknown, but Zaias [60] suggests that the deformity is usually due to self-inflicted trauma resulting from a tic or habit. Pressure repeatedly exerted on the base of the nail probably explains the appearance of this condition as well as its enlarged reddish lunula.

**Differential diagnosis**

A central longitudinal depression is found in “washboard nail plates” [96] caused by chronic, mechanical injury. This is also known as a onychotillomania [97]. Unlike Heller’s dystrophy, the cuticle is pushed back and there is accompanying inflammation of the proximal nail fold. Splits due to trauma, or those occurring in the nail–patella syndrome and in pterygium, are generally

![Figure 2.21](image-url) Median canaliform (Heller) dystrophy: (a) early; (b) later; (c) inverted “fir-tree” appearance, reaching the distal edge.
obvious. Longitudinal splits may also result from Raynaud disease, lichen striatus, and trachyonychia.

**Treatment**
Nail wrapping (Chapter 19) may reduce the disability produced by the fissure. Higashi et al. [98] considers that onychorrhexis with nail splitting is caused by micro-trauma to the proximal nail fold and suggest that topical steroid ointment should be applied on the fold.

**Longitudinal ridges** (Fig. 2.22)
Small rectilinear projections extend from the proximal nail fold as far as the free edge of the nail; or they may stop short. They may be interrupted at regular intervals giving rise to a beaded or sausage-like appearance often observed in psoriasis. Sometimes a wide, longitudinal median ridge has the appearance, in cross-section, of a circumflex accent. This condition, usually post traumatic, may be inherited and affects mainly the thumb and fingers of both hands.

**Oblique lines/chevron nail/herringbone nail**
(see Chapter 10)
In early childhood, the ridges may be oblique and converge towards the center distally. Sometimes, in teenagers one longitudinal half of the nail may present oblique lines while the other half is covered with longitudinal ridges. In this nail plate pattern, the lines form a V-shaped bar or bars [99]. The oblique lines disappear by adult life, in contrast to the gorilla, in which they are life long. The lines can be subtle and are best viewed with oblique lighting [100]. The significance of chevron nail [101] or herringbone nail [102] is still debatable.

**Transverse grooves and Beau’s lines**
(Figs 2.23–2.25)
Transverse lines in the form of sulci, limited proximally by slightly elevated ridges and affecting the surface of all nails at corresponding levels, were described by Beau in 1846 as “retrospective indicators” of a number of pathological states. The condition is sometimes restricted to the thumbs and great toes. The grooves are superficial, but more marked in the middle aspect of the nail.

The transverse depression, sometimes involving the whole depth of the nail plate, appears some weeks after illness (e.g. fever). As the approximate growth rate is known (Chapter 1), it is possible to assess the approximate time of the prior causative disease which has marked the nails: the thumbnail supplies information for the previous 5–6 months and the great toenail evidence of disease for up to 2 years. As the thumb nails and toenails are most frequently affected they are the most reliable indicators of previous disease. Markings occur inconsistently on the other digits.

Beau’s lines reflect a temporary reduction in matrix activity. The length in the long axis of the furrow represents the exact duration of the disease which has affected the matrix, and the distal limit of the depression, if abrupt, indicates a sudden attack of disease, and if sloping a more protracted onset. If the activity of the entire matrix is inhibited for a period of 1–2 weeks for example, Beau’s line will reach its maximum dimension causing a total division of the nail plate. Only the keratinized nail bed fills the gap between the old and new plate. This is seen in latent onychohadesis (Fig. 2.25) and leads to a
Physiological Beau’s lines may occur in 4–5-week-old babies, marking the transition from intrauterine to extrauterine life, and monthly with each menstrual cycle. Cyclic transverse nail grooves occurring simultaneously with groups of knots in the hair have been reported [104]. Beau’s lines may be due to any severe disability and, particularly, to measles in childhood; zinc deficiency, whatever the cause, may produce transverse grooves. Beau’s lines associated with hand–foot–mouth disease and Kawasaki disease have been reported in children [105, 106]. Antimitotic drug therapy temporarily inhibits the activity in nail matrix leading to transverse nail depression. In the interval between two series of chemotherapy, the nails are normal [107]. Beau’s lines have been reported in association with a variety of medications, including azathioprine, itraconazole, and octreotide [108–112].

In a study by Bellis and Nickol [113], Beau’s lines were noted in 33% of 52 members of an expedition to the Nepal Himalayas 8 weeks after return to low altitude. These changes can be considered a variant of “Everest nails,” first described by Hutchison and Amin [114], and described elsewhere in this chapter. The exposure to hypobaric hypoxia was suspected to affect nail matrix activity. Beau’s lines have also been observed after deep saturation dives in eight divers [115].

Transverse depressions restricted to one or two digits may indicate one of the following causes: injury, carpal tunnel syndrome, or extremes of cold in Raynaud disease. Unilateral Beau’s line may develop after hand trauma involving damage to nerves and flexor tendons [116] or after fractured and immobilized wrist [117, 118] or olecranon [119].

Lee and Yun [120] reported a case in which a 36-year-old man developed Beau’s lines on all five fingers of the same hand which sustained a fingertip crush injury limited to the thumb. They postulated that the changes on multiple fingers could be the result of physiological changes that accompanied the injury, immobilization after surgical therapy, or temporary hypoperfusion of the extremity secondary to tourniquet use during surgical therapy.

In addition to Beau’s lines, pseudo-pyogenic granuloma may follow hand trauma [121]. Beau’s lines and periungual pyogenic granulomas have also been described in a 9-year-old child after complex and serious medical illness and management in an intensive care unit [122]. A unilateral Beau’s line has also been observed in childhood reflex sympathetic dystrophy [123]. A transverse groove is the most common ischemic deformity of the nail seen by hand surgeons following the use of the upper extremity tourniquet [124]. Fine transverse grooves, a few millimeters wide, and starting at one lateral edge of the nail plate, may appear on the whole length from its proximal part to the free margin and may
occur in chronic paronychia; they may be dark or have a greenish tinge. Transverse depressions may be the consequence of a chronic condition, such as eczema. When a series of transverse grooves parallels the proximal fold rather than the distal convex curve of the lunula, the cause is likely to be repeated injury to the matrix from overzealous manicuring [94]. The grooves are separated by ridges of healthy nail. Beau’s lines are often reported in association with retronychia [125].

A habit–tic deformity of repeatedly pushing back the cuticle on one or several fingers can create “washboard nails” [97], a variant of habit–tic deformity. Usually the proximal nail fold of the thumb on the same hand is damaged by the index finger and shows redness, swelling, and scaling. This chronic mechanical injury results in a series of transverse grooves and a large central depression running down the nail (Fig. 2.26). When the central depression does not exist, psoriasis should be suspected. Habit–tic deformity may respond to treatment with a serotonin reuptake inhibitors [126], which is an antidepressant therapy for obsessive–compulsive disorders.

The “serrated koilonychia” syndrome consists of a combination of saw-like transverse grooving of all nails with koilonychias [3].

Total lack of nail plate synthesis may be preceded by a transverse band of leukonychia [127]. This indicates that initially the agent, such as a drug, caused only defective keratinization resulting in a white line. More severe disturbance results in matrix arrest and Beau’s line formation. Shoreline nails are vivid evidence of their prior drug-induced erythrodermas.

To explain how transverse ridging appears, Higashi [128] considers that the direction of nail growth is determined by three forces, that is, upward force due to the nail matrix, downward due to the proximal nail fold, and outward due to the nail cul-de-sac. The former does not change because the length of the matrix is fixed. The downward force fluctuates by the retraction and protrusion of the proximal nail fold, and the outward force fluctuates because the length of the cul-de-sac changes by the retraction and protrusion of the latter. The decrease of the downward force due to the retraction of the proximal nail fold results in thickening of the nail plate. The increase of the downward force due to protrusion of the proximal nail fold results in thinning of the nail. Consequently the fluctuation of the distal end of the proximal nail fold results in ridges and furrows of the nail plate. Topical steroid ointment applied on the proximal nail fold would be the right treatment.

Pitting (pits, onychia punctata, erosions, Rosenau’s depressions) (Fig. 2.27)

Pits develop as a result of defective nail formation in punctate areas located in the proximal portion of the matrix. The surface of the nail plate is covered by small punctate depressions which vary in number, size, depth, and shape. The depth and width of the pits relates to the extent of the matrix involved; their length is determined by the duration of the matrix damage.

They are randomly distributed or uniformly arranged in series along one or several longitudinal lines, or sometimes arranged in a criss-cross pattern; they may resemble the external surface of a thimble.

Samman [129] has shown that regular pitting could be converted to rippling or ridging (Fig. 2.28a) and these...
two conditions appear, at times, to be variants of uniform pitting. Nails showing pitting grow faster than the apparently normal nails.

Occasional pits occur on normal nails. Deep pits can be attributed to psoriasis. Shallow pits are usually seen in alopecia areata, eczematous dermatitis, lichen nitidus, or occupational trauma. In some cases a genetic basis is possible. In secondary syphilis and pityriasis rosea, pitting occurs rarely. We have seen one case of the latter, with the pits distributed on all the fingernails at corresponding levels, in a manner analogous to that of Beau’s lines.

Recently Di Chiacchio et al. [130] described “pseudo-pitting” of the nail in psoriasis, in which the pitting was located only above the oil drop signs or salmon patches within psoriatic nails.

**Trachyonychia and vertical striated sandpapered nail dystrophy** (Figs 2.29, 2.30) [131]

See Chapters 10 and 14.

**Pseudomycotic nail dystrophy** *(pseudomycotic onychia)*

Four cases of isolated pseudomycotic nail dystrophy were studied by Higashi et al. [132]. All the fingernails and toenails were simultaneously involved. Clinical features include longitudinal striations, fissuring, and scaling of the surface of the nail plate with sometimes a yellow-brown discoloration.

The epithelium of the nail matrix reveals hyperplasia with a granular layer and projections similar to the crest of a wave. Inflammatory cell infiltration is present at the upper dermis of the matrix. The nail plate consists of normally keratinized layers and abnormal ones in stratiform pattern.

These findings differ histologically from those of psoriasis, lichen planus, and twenty-nail dystrophy. Because of the inflammatory response of the matrix, Higashi et al. suggest the term “pseudomycotic onychia.” The significance of isolated pseudomycotic nail dystrophy is not known; however it seems difficult to completely rule out alopecia areata restricted to the nail, a condition in which the severe changes are sometimes “simulating longstanding onychomycosis” [133]. Milligan et al. [134] reported two cases involving all the digits, associated with vitiligo.

**Lamellar nail splitting** *(onychoschizia lamellina)*

In this condition, found in 27–35% of normal adult women, the distal portion of the nail splits horizontally (Fig. 2.31). The nail is formed in layers analogous to the formation of scales in the skin; the thin lamellae then break off. Exogenous factors contribute to the defect. It is common in people who carry out a great deal of housework, whose nails are repeatedly soaked in water and then dried. Splitting into layers has been reported in X-linked dominant chondrodysplasia punctata [135]) and in polycythemia vera [136]. In lichen planus, and in psoriasis treated with systemic retinoids, onychoschizia may be seen in the proximal portion of the nail [137].

Shelley and Shelley [138] studied with scanning electron microscopy the distal ends of nails of four women
Physical Signs

presenting with onychoschizia. The dorsal surface and tip of each nail showed horizontal lamellar separations representing single cell layers. Some cleavage lines extended proximally into the nail plate, revealing remarkable sculptured cell surfaces deep within the plate. These observations indicate that the lamellar splitting of onychoschizia occurs between cell layers. This presumably results from repeated trauma to a nail with diminished adherence between cell layers, secondary to the dissolution of intercellular cement by detergents and nail polish solvent.

Wallis et al. [139] studied the in vitro nail changes produced by several organic solvents, detergents, other polar materials, and both acidic and basic solutions. Although other factors may influence onychoschizia, the typical changes can be produced in normal nails after a 21-day challenge of repeated exposure to water followed by dehydration. Scanning electron microscopy demonstrated unattached individual cells in empty spaces in which separation was prominent. The prominent in vitro changes from wetting and drying suggest that lamellar dystrophy could be managed by hydration followed by an occlusive topical agent that promotes water retention. Wallis et al. [139] has successfully combined protection from exposure with hydrophilic petrolatum (Aquaphor) as a nail cream applied to the wet nails to maintain a relatively constant level of hydration. Lamellar onychoschizia has been reported in a female Chinese tea picker. In this case, the lamellar onychoschizia was limited to the right thumbnail, and the tea-picking maneuver involved holding the leaves between the right thumbnail and index finger. This work was seasonal, and the onychoschizia would resolve after the work was completed. The onychoschizia was speculated to be caused by either frequent wetting and drying of the nails or exposure to catechin, an acid in the tea [140].

Elkonyxis (Fig. 2.32)

Initially the nail appears punched out at the lunula and subsequently the disorder moves distally with the growth of the nail. It has been described in secondary presenting with onychoschizia. The dorsal surface and tip of each nail showed horizontal lamellar separations representing single cell layers. Some cleavage lines extended proximally into the nail plate, revealing remarkable sculptured cell surfaces deep within the plate. These observations indicate that the lamellar splitting of onychoschizia occurs between cell layers. This presumably results from repeated trauma to a nail with diminished adherence between cell layers, secondary to the dissolution of intercellular cement by detergents and nail polish solvent.

Wallis et al. [139] studied the in vitro nail changes produced by several organic solvents, detergents, other polar materials, and both acidic and basic solutions. Although other factors may influence onychoschizia, the typical changes can be produced in normal nails after a 21-day challenge of repeated exposure to water followed by dehydration. Scanning electron microscopy demonstrated unattached individual cells in empty spaces in which separation was prominent. The prominent in vitro changes from wetting and drying suggest that lamellar dystrophy could be managed by hydration followed by an occlusive topical agent that promotes water retention. Wallis et al. [139] has successfully combined protection from exposure with hydrophilic petrolatum (Aquaphor) as a nail cream applied to the wet nails to maintain a relatively constant level of hydration. Lamellar onychoschizia has been reported in a female Chinese tea picker. In this case, the lamellar onychoschizia was limited to the right thumbnail, and the tea-picking maneuver involved holding the leaves between the right thumbnail and index finger. This work was seasonal, and the onychoschizia would resolve after the work was completed. The onychoschizia was speculated to be caused by either frequent wetting and drying of the nails or exposure to catechin, an acid in the tea [140].

Elkonyxis (Fig. 2.32)

Initially the nail appears punched out at the lunula and subsequently the disorder moves distally with the growth of the nail. It has been described in secondary
Modification of the nail plate
and soft tissue attachments

The proximal nail fold is closely applied to the dorsal surface of the newly formed nail plate. At the free border of the proximal nail fold, the cuticle should adhere to the dorsal surface of the nail and seal the cul-de-sac. Inflammation of the proximal nail fold is called paronychia and will be described elsewhere; when this condition becomes chronic, the cuticle disappears and a "pocket" is created between the ventral surface of the posterior nail fold and the nail.

Pterygium

Pterygium of the nail has been described on both dorsal and ventral aspects of the nail plate. The term pterygium, which literally means "wing," is more suitable for the dorsal pterygium ("pterygium unguis"), which looks somewhat like a wing. It consists of a linear forward growth of the proximal nail fold which fuses with the underlying matrix and subsequently with the nail bed dividing the nail plate in two (Fig. 2.33a). Ventral pterygium represents the same process extending from the hyponychium, anchoring to the undersurface of the nail plate with subsequent obliteration of the distal nail groove. Both conditions are non-specific abnormalities of the nail apparatus.

Dorsal pterygium (see Appendix)

Dorsal pterygium or pterygium unguis consists of a gradual shortening of the cul-de-sac of the proximal nail fold with associated thinning of the nail plate until the latter becomes fissured because of the fusion of the proximal nail fold to the matrix and subsequently to the nail bed; the divided nail plate portions progressively decrease in size as the pterygium widens, resulting in two small remnants where the median part lateral segments. Complete involvement of the matrix and nail bed will produce a total loss of the plate and a permanent atrophy of the nail apparatus. It usually affects the fingers, rarely the toes [145]. Involvement of all 20 nails has been reported in one single case only [146] but can be observed in graft-versus-host disease. It is mostly acquired but exceptional congenital forms are reported. The first description was made by Friedman in 1921 under the term of "Navellierungsprozess" in a case of nail lichen planus.

Lichen planus remains its major cause [147] (Fig. 2.33b), but pterygium unguis has also been reported in isolated instances in various conditions. Healing of a disease involving the proximal nail fold may lead to pterygium formation as a scarring sequel. Physical factors such as trauma [148], burns, radiodermatitis [149], and diseases prone to develop adherence bands such as cicatricial pemphigoid [150], graft-versus-host disease [151], toxic epidermal necrolysis [152], and pemphigus foliaceus may be etiological. There may be vascular causes such as peripheral ischemia, which can be intermittent as in Raynaud phenomenon [145] or permanent as in atherosclerosis and diabetic vasculopathy [153] and type 2 lepra reaction [154]. An idiopathic form called "idiopathic atrophy of the nails" has been reported and is probably a variant of lichen planus but remains controversial [155]. There are congenital forms possibly associated with dyskeratosis congenita. Pterygium formation has also been reported in one case of sarcoidosis involving the proximal nail fold [156] and in systemic lupus erythematosus. A patient with Marfan syndrome also showed this finding, and a nail unit biopsy showed a scant inflammatory infiltrate [157]. Dorsal pterygium has also been seen with...
porokeratosis of Mibelli affecting the nail unit [158]. A variant of onychomatricoma, associated with dorsal pterygium, in three cases has been described. Dorsal pterygium resulted from matrix metaplasia of the ventral aspect of the proximal nail fold [159].

It seems that several coincident factors are required to produce pterygium formation. In patients with dorsal pterygium (except of the traumatic or congenital type), the main characteristic is a dilatation of the nail capillary loops and the formation of a slender microvascular shunt system in the more dilated loops. Pterygium resulting from trauma is not linked to its intensity; it may be observed in severe distal injury, it remains exceptional in repeated chronic trauma inflicted to the proximal nail fold in onychotillomania [160]. Treatment of pterygium unguis remains very difficult and requires surgery: the nail plate is elevated from the dorsum of the nail bed and held separated with a strip of silastic or non-adherent material. This allows the undersurface of the nail fold to epithelialize. If unsuccessful, a split-thickness graft should be placed on the undersurface of the proximal nail fold after freeing it from the nail plate [161]. If surgery is refused by the patient, injections of corticosteroids within the whole length of the pterygium may stop its progression and may even cause some flattening.

**Ventral pterygium** [162–176] (see Appendix)

Ventral pterygium is a relatively recently described condition: the term pterygium inversum unguis was first coined by Caputo and Prandi [162] to describe a condition consisting of a forward extension of the hyponychium anchoring to the undersurface of the nail plate and thus obliterating the distal nail groove (Fig. 2.34). The similarity in the behavior of the hyponychium and proximal nail fold in the two conditions led to the similarity of the name. However, the ventral pterygium does not look like a wing and does not split the nail.

Pterygium inversum unguiis may be either congenital or acquired. The congenital form was first described by Odom et al. [163] as a “congenital, painful and aberrant hyponychium.” In some instances, the condition has been reported as familial [164–166]. In most reported cases the patients sought medical advice for pain or bleeding when trimming their nails [162, 165, 167, 169]. Involvement of the toes remains exceptional: it may be associated with fingernails [167, 169]; restriction to the toes has been reported once only [166]. Women are more prone to develop this condition [167].

By far the commonest form of pterygium inversum unguiis is the acquired form [170–174]. It may sometimes be idiopathic but it is generally secondary to systemic connective tissue diseases and particularly to progressive systemic sclerosis and systemic lupus erythematosus. Its occurrence in patients with such diseases has been estimated to be 16%. Furthermore, one patient with congenital pterygium inversum unguis developed systemic lupus erythematosus at the age of 19 years.

Pterygium inversum unguiis has also been described in various other conditions. Zaias et al. [161] have proposed a new nomenclature based on tissue origin and pathology to account for these conditions: (i) congenital aberrant hyponychium; (ii) acquired pterygium inversum unguis; (iii) acquired reversible extended hyponychium (Fig. 2.35a,b).

The pathogenesis of pterygium inversum unguis remains unclear. The congenital form could be related to an early defect in the developing fetal groove and ridge [163] or considered as a vestigial remnant of the animal claw [162]. Histological findings from the case reported by Vadmal et al. [175] demonstrated marked hyperkeratosis, with a few foci of parakeratosis, that extended up to and firmly attached to the ventral surface of an unremarkable nail plate. Another biopsy of pterygium inversum unguiis demonstrated a marked highly eosinophilic keratinized substance attaching the distal and visceral nail plate. This substance contained distinct pale nucleated corneocytes. An eosinophilic whorled keratinized substance was seen in the horny layer of the fingertip. The authors from this study believed that the eosinophilic material seen in the specimen was derived from the nail isthmus, a functionally distinct region of the nail unit located between the nail bed and the hyponychium [176].
Medical treatment for pterygium inversum unguis has not been rewarding: twice daily application of tretinoin 0.05% was useless [163] and electrocautery was followed by recurrence [169]. However, an extensive case obtained a good therapeutic response with hydroxypropyl chitosan [177]. Therapy directed towards the improvement of impaired peripheral blood flow (α-methyldopa, Aldomet) in patients with scleroderma and Raynaud phenomenon, while improving the latter, did not affect the nails [165]. Surgery may be more useful and usually provides relief from pain: after avulsion of the distal 5-mm nail, a strip of nail bed and hyponychium 3–4 mm wide is resected and replaced by a split-thickness graft.

Onychomadesis/nail shedding/nail degloving
(Figs 2.36, 2.37) (see Appendix)

Spontaneous separation of the nail from the matrix area with persistent attachment to the nail bed [178–182] is called onychomadesis. At first, a cleavage appears under the proximal portion of the nail, followed by the disappearance of the juxta-matrical portion of the surface of the nail. A sort of surface ulcer is thus formed, which does not usually involve the deeper layers. This is due to a limited lesion of the proximal part of the matrix. In latent onychomadesis [103] the nail plate shows a transverse split (Fig. 2.25) because of transient complete inhibition of nail growth for at least 1–2 weeks. It may be characterized by a Beau’s line which has reached its maximum dimension; nevertheless the nail continues growing for some time because there is no disruption in its attachment to the nail bed. Growth ceases when it is cast off after losing this connection. In some very severe general acute diseases, such as Lyell syndrome, the proximal edge of all the nail plates may be elevated. Onychomadesis has been associated with infection, autoimmune disease, critical illness, and medications.

Retronychia (Fig. 2.37a,b) is the term coined by de Berker and Rendall [183] for describing a proximal nail embedding as an acute onychomadesis involving patients with a 3–6-month history of inflammation in the affected digits. After ineffective conservative treatment, avulsion may reveal three generations of nail joined distally but separate proximally, with the upper and oldest generation embedded into the overlying proximal nail fold. Interestingly other nails on the hands may present Beau’s line with onset synchronous with the thumb pathology in one case. All cases arose following a precipitating event altering the nail growth; bilateral in the first two and minor trauma in the third. Failure of longitudinal growth combined with a wedge-like effect of new nail beneath directed the overlying nail upwards into the proximal nail fold. This non-recurrent pathology resolves by loss of the nail and may be due to latent onychomadesis with nail retention favored by posterolateral ligamentous attraction of the plate (see Chapter 22).

Ultrasound has demonstrated a shortening of the distance between the origin of the nail plate and the base of the distal phalanx [184].

The terms nail shedding [177], onychoptosis defluvium, or alopecia unguium, are sometimes used to describe atraumatic nail loss. Onychomadesis usually results from serious generalized diseases, bullous dermatoses, hand–foot–mouth disease, Kawasaki disease, drug reactions, intensive X-ray therapy, acute paronychia, severe psychological stress, or it may be idio-pathic. Recently, onychomadesis has been associated with the use of valproic acid, azithromycin, and capecitabine. When the disease is inherited (as a dominant characteristic) the shedding may be periodic, and rarely associated with the dental condition amelogenesis imperfecta. Longitudinal fissures, recurrent onychomadesis, and onychogryphosis may be associated with mild degrees of keratosis punctata. In toenails, onychomadesis may be produced by minor traumatic episodes,
Figure 2.36 (a) Lyell syndrome periungual bullae. Courtesy of S. Goettmann-Bonvallot. (b) Lyell syndrome onychomadesis. Courtesy of S. Goettmann-Bonvallot. (c) Nail shedding, onychomadesis type. Courtesy of A. Krebs. (d) Lyell syndrome onychomadesis with early nail shedding. (e) Lyell syndrome nail deglovement. Courtesy of S. Goettmann-Bonvallot. (f) Lyell syndrome late stage.
as in sportsman’s toe. Onychomadesis and pyogenic granuloma following cast immobilization have been reported by Tosti et al. [179]. Onychomadesis has been reported in neonates in association with both stress related to breech position before delivery and a normal vaginal delivery [180, 181]. Piraccini et al. [182] described a patient with Cronkhite–Canada syndrome who developed recurrent onychomadesis related to acute episodes of the disorder. Total nail loss with scarring may be due to permanent damage of the matrix following trauma, or late stages of acquired onychatrophia following lichen planus, bullous diseases, or where there is defective peripheral circulation. In texts on congenital anomalies, this defect is sometimes referred to as aplastic anonychia, which does not always produce scarring. Temporary total nail loss may also result from severe progressive onycholysis.

Degloving (see Appendix)

The nail degloving syndrome described by Baran and Perrin [185] refers to partial or total avulsion of the nail and surrounding tissue (see Chapter 10). It represents the final stage of damage to the nail unit from multiple causes, including trauma, dermatological disorders, and drug reactions. Three patterns of nail degloving are described. In typical thimble-shaped nail shedding, the walls of the thimble are composed of the skin of the distal digit including the nail plate (circumferential skin shedding). The second pattern is described as a partially sloughed off nail plate with surrounding tissue. In the third pattern the nail shedding involves the entire nail apparatus and its components, but spares the surrounding epidermis of the distal digit. Nail degloving results from weakness at the dermal–epidermal junction. In lichen planus and toxic epidermal necrolysis, this is caused by vacuolar degeneration and cell death in this anatomical location. In gangrene, damage to the nail unit resulting in degloving is caused by papillary edema and ischemic necrosis secondary to vascular thrombosis. In nail degloving, the most proximal areas of the ventral aspect of the proximal nail fold and proximal matrix remain attached to the native nail unit, and are not lost. Subsequent to nail degloving, it is possible to have recovery with normal nail growth.

Onycholysis (see Appendix)

Onycholysis refers to the detachment of the nail from its bed at its distal end and/or its lateral attachments (Fig. 2.38). The pattern of separation of the plate from the nail bed takes many forms. Sometimes it closely resembles the damage from a splinter under the nail, the detachment extending proximally along a convex line, giving the appearance of a half moon. When the process reaches the matrix, onycholysis becomes complete. Involvement of the lateral edge of the nail plate alone is less common. In certain cases, the free edge rises up like a hood, or coils up itself like a roll of paper (Fig. 2.39). Onycholysis creates a subungual space that gathers dirt and keratin debris. Water accumulates in the “cave” beneath the nail plate and secondary infection by bacteria and yeasts occurs. As opposed to chronic paronychia, inflammation is rarely seen [186]. The greyish-white color is due to the presence of air under the nail but the color may vary from yellow to brown, depending on the etiology. This area is sometimes malodorous.

Daniel et al. [187] have described the phenomenon known as the “disappearing nail bed,” which can occur...
with longstanding onycholysis. The nail bed appears to shrink, and the area becomes keratinized, develops a granular layer, and produces dermatoglyphics as is seen on the normal tip of the digit. As the nail bed contributes a portion of the structure of the nail plate, the nail plate which is produced in such an affected area has a soft ventral aspect, which may not attach well to the nail bed. A grading system for onycholysis has also been proposed, which ranges from stage I, with early initial separation of 1–2 mm of the distal nail plate from the hyponychium, to stage V, which demonstrates the disappearing nail bed.

In psoriasis there is usually a yellow margin visible between the pink, normal nail and the white separated area. In the “oily spot” or “salmon-patch” variety, the nail plate–nail bed separation may start in the middle of the nail; this is sometimes surrounded by a yellow margin. The accumulation of large amounts of serum-like exudate containing glycoprotein, in and under the affected nails [60], explains the color change in this kind of onycholysis. Glycoprotein deposition is commonly found in inflammatory and eczematous diseases affecting the nail bed. Oil patches have been reported in systemic lupus erythematosus; they may be extensive in leucitis purulenta and granulomata. Onycholysis is usually symptomless and it is mainly the appearance of the nail which brings the patient to the doctor; occasionally there is slight pain associated with inflammation in the early stages. The extent of onycholysis increases progressively and can be estimated by measuring the distance separating the distal edge of the lunula from the limit of proximal detachment. Transillumination of the terminal phalanx gives a good view of the area [188].

The onset of onycholysis may be sudden, as in photoonycholysis [189] (Chapter 16), when there may be a triad of “photosensitization, onycholysis and dyschromia” [190], or when the cause is contact with chemical irritants such as hydrofluoric acid [191] or rust-removing agents [192]. Sculptured onycholysis [60] is a self-induced nail abnormality produced by cleaning the underside of the nail plate with a sharp instrument. This results in an opaque, dead portion of the nail with a gently curved proximal “lytic” border. A related entity is mechanical onycholysis, which was described by Piraccini et al. [193] in a 7-year-old girl who had been repetitively inserting and rubbing a thin paper sheet under the nail plate, damaging the onychodermal band and causing onycholysis.

Therapies for onycholysis include keeping the nails clipped short and meticulous nail care, and can include the use of broad spectrum topical antifungals. Daniel et al. [194] treated 31 patients with onycholysis with a regimen of ciclopirox 0.77% topical suspension administered to the affected areas twice daily for 6–12 weeks in combination with a strict irritant avoidance regimen; 87% of patients showed improvement and 81.5% showed total clearance. For docetaxel-induced onycholysis, use of a frozen glove has been demonstrated to be an effective therapy. Two patients with chronic onycholysis demonstrated improvement with increased intake of carotene-rich foods [195].
Onycholysis of the toes demonstrates some differences from the condition on the fingers. The major distinctions are governed by the lack of occupational hazards; the reduced use of cosmetics on the feet; and the protection afforded by footwear, which reduces the risk of photoonycholysis.

The two main causes of onycholysis of the toenail, especially the great toenail are: (i) onychomycosis and, above all, (ii) repeated minor traumas. Primary candida onycholysis is almost exclusively confined to the fingernails and is most common in women [196].

Traumatic onycholysis may have a different presentation, as follows.

1) The diagnosis is conspicuous when the nail is lifted up by a blister after strenuous exercise in new footwear, not necessarily platform shoes. The blister may have disappeared leaving an oozing nail bed. Sometimes there is only a blackish hue or thorough examination finds a distal worn-down great toenail.

2) Sometimes the diagnosis is not self-evident. A careful search must be made to look for a discrete brownish tinge, the signature of the trauma.

3) In distal and subungual onychomycosis of the toenails, the horny thickening raises their free edge with disruption of the normal nail plate–nail bed attachment; this gives rise to secondary onycholysis in this common presentation.

Baran and Badillet [197] have questioned whether great toenail onychomycosis is ever truly primary. Its presence should always lead to a search for abnormalities of the foot, such as hyperkeratosis of the metatarsal heads, large thickening of the ball of the foot, or pressure on the great toe by an overriding second toe, this being fully developed when shoes are worn. All these disorders are frequently combined with high heels and narrow and slanting shoes. A silicone rubber molded toe cap or a silicone rubber orthodigital splint or a direct molding splint, the device being produced in situ, can be helpful.

Interestingly, Zaias et al. [198] examined 49 dermatophyte-negative subjects. All demonstrated skeletal and toenail unit abnormalities. The clinical toenail unit abnormalities of the asymmetric gait syndrome include onycholysis, nail bed keratosis, nail plate surface abnormalities, and a diagnostic nail plate shape; this is referred to as the asymmetric gait unit syndrome (AGNUS) and is indistinguishable from distal subungual onychomycosis. Early recognition of the characteristic toenail signs, which have their onset in the early years, getting worse with age, may contribute to the health and quality of life of the unsuspecting subject who has some skeletal correctable abnormalities.

In summary, the two entities appear clearly distinct, except when onycholysis seems the primary disease and is accompanied by both dermatophytes and plantar anomalies. In such cases, the dermatophytes may act as commensal agents and we suggest that therapy should above all remove the pressure and help to restore proper balance to the foot with fitted shoes and padding or accommodative shields.

Subungual hyperkeratosis

Besides congenital nail bed hyperplasia, epithelial hyperplasia of the subungual tissues results from exudative skin diseases and may occur with any chronic inflammatory condition which involves this area (Fig. 2.40). It is especially common in psoriasis, pityriasis rubra pilaris, and chronic eczema, or it may be due to fungi. Histology reveals PAS-positive, homogeneous rounded- or oval-shaped amorphous masses surrounded by normal squamous cells usually separated from each other by empty spaces. These clumps, which coalesce and enlarge, have been described by Zaias [60] in psoriasis of the nail. They are also found in some hyperkeratotic processes such as warts involving the subungual area. Squamous cell carcinoma of the nail unit can present with subungual hyperkeratosis. Subungual epidermoid inclusions (subungual onycholemmal cysts) can also present with subungual hyperkeratosis [199]. Subungual keratosis may also be seen in lichen planus, lichen striatus [200], reactive arthritis, Sézary syndrome, Langerhans cell histiocytosis, sarcoidosis, pityriasis rubra pilaris, discoid...

![Figure 2.40](image-url) Huge subungual keratosis lifting up the normal nail plate.
lupus erythematosus [201], Darier disease, and Norwegian scabies. Painful subungual hyperkeratosis in patients with incontinentia pigmenti can represent keratoacanthoma [202]. The horny excrescences of the nail bed are not very marked but the ridged structure may become apparent if the nail plate is cut shortened.

In *keratosis cristarum* [18] the keratinizing process is limited to the peripheral area of the nail bed (Fig. 2.41). It starts at its distal portion but may progress somewhat proximally. Acaulis (*Scopulariopsis onychomycosis*), which may present similar alterations, should be ruled out.

Localized multinucleate distal subungual keratosis [203] may produce a small horny lesion originating from the hyponychium or the distal nail bed. This condition is sometimes associated with erythronychia (*onychopapilloma of the subungual tissue*) (Chapters 4 and 21).

**Modification in perionychial tissues**

Paronychia, ingrowing nails, tumors of the nail folds, and periungual telangiectasia is each described in the appropriate sections. In chronic paronychia, the attachment of the proximal nail fold to the underlying nail plate by the cuticle is interrupted. Formation of a real space from a potential space results where irritants and water accumulate [186].

Thickened, hyperkeratotic, irregular (“ragged”) cuticles have been reported, especially in dermatomyositis. Pushing them back is painful (“Keining-Zeichen” [204]), but may be seen in normal careless individuals. Thickened cuticle composed of several layers and called “polyeponychia bolboides” (onion-like) by Happle and Chang [205] can be an unusual manifestation of factitious disorders.

Perionychial tissues are subject to trauma, such as rubbing of the proximal nail fold of the great toenail against the roof of the shoes. There may be self-inflicted erosions of the nail folds in association with neurosis. The ulnar side of the nail is most vulnerable and there may be small, triangular tags of epidermis (“hang nail”) which are painful and vulnerable to secondary infection. Hang nails may also result from occupational injuries.

Painful dorsolateral fissures (Fig. 2.42a) may develop distal to the lateral nail groove when there is a combination of factors such as frequent wetting, dry skin, and the winter months [206]. Sometimes these fissures converge to the tip of the finger. They also can be observed in atopic and psoriatic patients (Fig. 2.42b) and as occupational disorders in cement workers.

The causes of paronychias are listed in the Appendix.

**Modification in the consistency of the nail**

The nail plate is a unique combination of strength and flexibility. It may be hard, soft, brittle, or friable. The following definitions should be remembered [207].

1) *Strength* is the ability of the nail plate to withstand breakage.
2) *Stiffness/rigidity/hardness* measures how easily the plate is scratched or indented.
3) *Flexibility* determines how much the plate will bend. It is due to moisture content.
4) *Brittleness* shows how likely the nail is to break.
5) *Toughness* is a combination of strength and flexibility.

*Hard nails* are seen in pachyonychia congenita. They must be soaked for prolonged periods before they can be trimmed; large, “professional” nail clippers are most suitable for this purpose. Jadassohn, who first described this syndrome, had to use a hammer and chisel on the hardened nails of his patient. For very soft nails the term hapalonychia is used. Such nails may be thinner than usual (less than 0.5 mm) and bend easily, and break or split at the free edge. In some cases the nails, which assume a semitransparent, bluish-white hue, are referred to as “egg-shell nails.” Hapalonychia has been noted in chronic arthritis, leprosy, myxedema, acrosyphasia, peripheral neuritis, hemiplegia, cachexia, and other...
states. Occupational contact with chemicals is probably the most common cause. **Soft nail disease** [208] is an unusual, congenital, nail dystrophy with anatomical and functional defects of the nail matrix.

The **nail fragility syndrome**, also called “brittle nail syndrome,” encompasses six main types [207]:

1) **Onychorrhexis** consists of shallow parallel furrows running in the superficial layer of the nail (Fig. 2.43a). It may result in an isolated split at the free edge, which sometimes extends proximally.

2) A single longitudinal split of the entire nail plate is sometimes observed. It may be produced by focal matrix lichen planus.

3) Multiple crenellated splitting, which resembles the battlements of a castle. Triangular pieces may easily be torn from the free margin (Fig. 2.43b).

4) Lamellar splitting of the free edge of the nail into fine layers (Fig. 2.31). It may occur in isolation or associated with the other types. Proximal lamellar splitting may occasionally be observed in lichen planus and during etretinate or acitretin therapy.

5) Transverse splitting and breaking of the lateral edge, usually close to the distal margin (Fig. 2.44).
6) The changes in brittle friable nails are often confined to the surface of the nail plate; this occurs in superficial white onychomycosis and may be seen after the application of nail polish or base coat which favors “granulations” in the nail keratin (Fig. 2.45a) (see Chapter 19). In advanced psoriasis (Fig. 2.45b) and fungal infection the friability may even extend throughout the entire nail.

Changes in nail consistency may be due to impairment of one or more of the factors on which the health of the nail depends and include such elements as variations in the water content or the keratin constituent. Changes in the intercellular structures, cell membranes, and intracellular changes in the arrangement of keratin fibrils have been revealed by electron microscopy [209]. Normal nails contain approximately 15% water. After prolonged immersion in water this percentage is increased and the nail becomes soft; this makes toenail trimming much easier. A low lipid content may decrease the nail’s ability to retain water. If the water content is considerably reduced, the nail becomes brittle. Splitting, which results from this brittle quality, is probably partly due to repeated uptake and drying out of water.

The keratin content may be modified by chemical and physical insults, especially in occupational nail disorders (Chapter 18). Amino acid chains may be broken or distorted by alkalis, oxidizing agents, and thioglycolates, such as chemicals employed in the permanent waving processes. These break or distort the multiple disulfide bond linkages which join the protein chains to form the keratin fibrils. Keratin structure can also be changed in genetic disorders [210]. In some congenital conditions, such as dyskeratosis congenita, the nail plate is completely absent, or reduced to thin, dystrophic remnants.

The composition of the nail plate is sometimes related to generalized disease. High sulfur contents predominate in the form of cystine, which contributes to the stability of the fibrous protein by the formation of disulfide bonds. A lack of iron can result in softening of the nail and koilonychia; conversely, the calcium content in the nail would appear to contribute little towards its hardness. Calcium is mainly in the surface of the nail, in small absorbed quantities, and X-ray diffraction shows no evidence of calcite or apatite crystals. Damage to both the central and peripheral nervous system may result in nail fragility.

A grading system for brittle nails has been proposed, and measures with a 0–3 scale the severity of changes of lamellar splitting, transverse splitting, ridging, longitudinal splitting, and nail thickness [211].

Figure 2.44 Transverse splitting of the lateral edges.

Figure 2.45 (a) Friability of the nail surface, here caused by nail cosmetic base coat. (b) Superficial friability in a psoriatic patient. Courtesy of B. Schubert.
Chapter 2

Causes of nail fragility (see Appendix)

Non-general causes

These may be local or, less frequently, systemic.

Local causes may be due either to nail plate impairment or to matrix impairment. The nail may be damaged by trauma or by chemical agents such as detergents, alkalis, various solvents, sugar solutions, and, especially, by hot water.

As the nail plate requires 5–6 months to regenerate it is therefore vulnerable to daily insults. Anyone carrying out a lot of household tasks is very susceptible; particularly at risk are the first three fingers of the dominant hand. Anything that slows the rate of nail growth will increase the risk. Cosmetic causes are rare. Some varnishes will damage the superficial layers of the nail. Drying may be enhanced by some nail varnish removers [212], and soaking fingers in a warm soapy solution to remove the cuticle is especially dangerous as this is common practice among manicurists. It has been shown that climatic and seasonal factors may affect the hydration of the nail plate.

Fragility, due to thinning of the nail plate, may be caused by a reduction in the length of the matrix. Diminution, or even complete arrest of nail formation over a variable width, may be the result of many dermatoses such as eczema, lichen planus, psoriasis (rare), and impairment of the peripheral circulation. The frequency of nail fragility in alopecia areata lends credence to the popular belief that nail and hair disorders are often associated.

Lubach and Beckers [213] have shown that in women the bridges between nail corneocytes are possibly weaker than in men as a constitutional characteristic. Accordingly, frequent, alternating periods of hydration and drying increase the incidence of brittle nails, particularly in women.

General causes

Among these are included hypochromic anemia, reduction in serum iron, arsenical intoxication, infection, diseases which produce severe generalized effects, arthritic deformities of the distal joints, deficiencies in vitamins A, C, and B6, osteoporosis and osteomalacia; also, there are numerous inherited defects associated with atrophy of the nail. The diverse constituents of the nail plate, especially the enzymes necessary for the formation of keratin, are subject to genetic influences and changes in them are manifested in the form of hereditary disease.

Treatment of brittle nails

Moisture (excess hydration) and trauma must be avoided at all cost; routine household chores are particularly damaging. Protection with rubber gloves worn over light cotton glove liners should be used in order to avoid frequent direct contact with water.

A warm environment and hyperemia may lead to faster growth. This could bring about a reduction in the time that the nail plate is exposed to repeated minor chemical and physical actions which accentuate nail fragility.

There is no efficient barrier cream able to prevent oversoftening of the nails due to water and detergents. After hydration, the nail plate should be massaged with mineral oil or a lubricating cream to prevent the nail from drying out. Low molecular mass natural oils that can penetrate and seal the upper surface of the nail plate, such as olive oil, rice brand, or jojoba oil, can be helpful [207]. Under experimental conditions hydration may be further enhanced by the addition of phospholipids, which have been shown to be effective in increasing and maintaining the increased nail flexibility [214]. This may result from an occlusive effect of the applications, which may delay the evaporation of water. Base coat, nail polish, and hard top coat act in a similar manner and also have a splint-like effect in strengthening the nail.

Some treatments claim to make the nails harder, for example by painting them daily with 5% aluminum chloride in propylene glycol and water. Such products make the nails stiff and brittle, which causes them to be less flexible and have lower strength.

There are two types of products which claim to harden nails. The first type encompasses modified nail polishes which include nylon fibers, acrylate resin, and hydrolyzed proteins. These products can function as a base coat, or as a solitary treatment. These products create a protective coating, and do not alter the structure of the nail plate. Other products are a modification of clear nail polish and can contain polyessters, acrylics, and polyamides, and function as a base coat to allow better adherence of a colored nail polish. The second type of nail hardener changes the structure of the nail plate itself. Such products may contain up to 5% formaldehyde tissue fixative. Formaldehyde causes cross-linking of the keratin and permanently alters the nail plate. Judicious use of formaldehyde-containing products is key, as adverse effects such as paronychia, onycholysis, subungal hyperkeratosis, dryness of the fingertips, and pterygium inversum can occur. Dimethyl urea is a nail-hardening ingredient that has advantages over formaldehyde: it is non-sensitizing and does not penetrate as deeply into the nail plate as formaldehyde. The effect of cross-linking is self-limited and reduces the potential for overhardening and embrittlement. Nail mending and nail wrapping are other alternative maneuvers to repair damaged or brittle nails.

Systemic treatment may be helpful. Zaun [215] demonstrated that brittle nails tested with a standardized micrometric method swell significantly less than normal nails: measurement of these “swelling properties” may be the best documented and most reliable method for the treatment of brittle nails. Qualitative assessment data
can also be obtained by scanning electron microscopy. Measurement of the transonychial water loss and assessment of the thickness and density of nails by ultrasound have also been used successfully.

Oral iron (given for 6 months), even in the absence of demonstrable iron deficiency, may be of some value. Iorizzo et al. [216] reported that iron supplementation may be very effective when ferritin levels are below 10 ng/mL. Campbell and McEwan [217] suggested the following regimen: evening primrose oil (Efamol G), two capsules three times a day; pyridoxine, 25–30 mg per day; and ascorbic acid, 2–3 g per day. Gelatin has been abandoned; more recently, biotin has been prescribed for brittle nails [218] and several studies have demonstrated its effectiveness. Biotin is a water‐soluble B complex vitamin that has been recommended to be taken at a dose of 2.5 mg per day. The recommended treatment time is 3–6 months, and, on average, clinical improvements can be seen after 2 months. Specifically, an increase in nail thickness, decreased lamellar splitting, and decreased irregularities of the dorsal nail plate have been documented [219].

Recently a study of topical ciclosporin versus emulsion vehicle for treatment of brittle nails showed improvement in both the topical ciclosporin and emulsion vehicle groups. The untreated nails did not improve [220].

Modification in color: nail dyschromia, or discoloration, or chromonychia (see Appendix)

The term chromonychia indicates an abnormality in color of the surface of the fabric of the nail plate and/or subungual tissues.

1) At first glance, when there is nail contact with occupationally derived agents or topical application of therapeutic agents, the discoloration often follows the shape of the proximal nail fold (Fig. 2.46a); if the discoloration corresponds to the shape of the lunula, internal causes predominate (Fig. 2.46b).

Generally abnormalities of color depend on the transparency of the nail, its attachment (presenting as subungual hyperkeratosis or onycholysis), and the character of the underlying tissues such as the state of the skin vessels, various intravascular factors (anemia, carbon monoxide poisoning, methemoglobinemia, and sulfhemoglobinemia).

The nail provides a long‐sustained historical record of profound temporary abnormalities of the control of skin pigment which might pass unnoticed.

2) Pigment may accumulate as a result of hyperproduction (melanin), storage (copper, various drugs), or surface deposition.

3) Subungual hematoma leads to the accumulation of blood that cannot be degraded to hemosiderin because it is located between the nail plate on top and the newly formed deeper nail plate portion from the more distal matrix. A narrow longitudinal hemosiderin band in the nail was described by Alkiewicz and Pfister [221], who demonstrated hemosiderin granules by Prussian blue staining. Small granules were intracellular; large globules intercellular.

4) Examination of abnormal nails should be carried out with the fingers completely relaxed and not pressed against any surface.

The fingertip should then be blanched to see if the pigmented abnormality is grossly altered; this may help to differentiate between discoloration of the nail plate and that of the vascular nail bed. If the discoloration involves the latter it will usually disappear.
5) Further information may be gleaned by transillumination of the nail using a pen torch placed against the pulp. The nail lesions for which transillumination is especially effective include varying degrees of nail plate markings, onycholysis, subungual thickening, and leukonychia. In a dark room, a single narrow strong beam of light is used underneath the flexor pad of the fingertip. The blackish lines of the nail plate, pits, separation of the nail plate, and thicknesses are seen and differentiated readily from the diffuse homogeneous reddish glow of the normal nail plate [222]. If the discoloration is located in the matrix or the soft tissue, its exact position can be more easily identified (e.g. glomus tumor).

6) To determine if the color is within the plate, a piece of nail should be cut off and examined while immersed in water. When nail specimens are allowed to dry, their true color may be obscured by light scattering. Furthermore, if a topical agent is suspected as the cause, one can remove the discoloration by scraping or cleaning the nail plate with a solvent such as acetone. However, if leaking of nail varnish is responsible for nail plate staining, the dyes may penetrate the nail too deeply to be removed. If the substance is impregnated more deeply into the nail or subungually, microscopic studies of potassium hydroxide preparations or biopsy specimens, using special stains such as Fontana–Masson silver stain, may be indicated. Wood’s lamp examination is sometimes useful, showing yellow lunulae with fluorescence after tetracycline therapy [223], or fluorescence of the nails from quinacrine hydrochloride [224]. Nail composition studies might be helpful in the future.

7) When the pigmentation involves all the digits and follows the shape of the lunula, it always results from the systemic absorption of a chemical through the lung, the gastrointestinal tract, or the skin. There are two possibilities: (i) the disappearance of the nail bed blanching test, which means that the pigment originates from the blood vessels (see also nail dyschromia in Chapter 18); (ii) the pigmentation, which is not altered on the nail blanching test, is obliterated by a pen torch pressed against the pulp, meaning that the pigment is deposited in the nail bed tissue.

Causes of color modification (see Appendix)

The causes of color modification are summarized in the following list; the subtypes within these broad groups are described in the chapters indicated or in the tables that accompany the list below.

1) Exogenous causes (see Chapters 15 and 18).
   a) Contact with occupationally derived agents (Chapter 18).
   b) Topical application of therapeutic agents (see Appendix).
   c) Tobacco, cosmetics, and miscellaneous (see Appendix).
   d) Traumatic causes (see Appendix).
   e) Physical agents (see Appendix).
   f) Fungal and bacterial chromonychia (see Chapter 12 and Appendix).

White discoloration of the nails is common with most fungal infections. The condition “superficial white onychomycosis” is an infection in which the initial invasion occurs from the top surface of the nail plate. The disease normally presents with invasion of the superficial aspect of the nail plate together with a powdery discoloration which is chalky white. Fungal hyphae are present on the top surface of the nail. The main causes of this condition are *Trichophyton mentagrophytes*, *Microsporum persicolor*, *Fusarium*, *Aspergillus*, and *Acremonium* spp. It has also been reported by Zaia [225] that *Candida albicans* may produce this pattern of nail plate invasion in infants. Superficial black onychomycosis has been reported with *Trichophyton rubrum* and *Neoscytalidium dimidiatum*.

The color of the nail in dermatophyte infections may also be yellow or brown, particularly in the case of *T. mentagrophytes*, which may result in streaky pigmentation of the great toenails. *Scopulariopsis brevicaulis* causes an infection of the toenails in which the color is a light cinnamon brown due to the pigmentation of the fungal spores in the nail keratin. *Acrothecium nigrum* and *Fusarium oxysporum* are said to cause a black-green discoloration of the nail. There are a large number of brown pigmented fungi and some of these cause nail disease, although it is possible that in some reported cases fungi may simply have colonized areas of onycholysis.

In fungal melanonychia the nail plate appears black but the pigment is often grouped into a cluster at the distal edge. The pigmentation has irregular density and is irregularly distributed. Fungal melanonychia may have more significance than just the gross pigmented anomaly. Black or dematiaceous fungi produce melanin which may affect virulence through enhancing resistance to phagocytosis. In addition melanin may also affect the outcome of antifungal chemotherapy. Melanin biosynthesis inhibitors such as tricyclazole may therefore contribute to the efficacy of chemotherapy.

It is likely that the production of melanin conveys an evolutionary advantage on fungi that live
in the natural environment; fungi that produce melanin are more resistant to the adverse effects of ultraviolet irradiation, heat, or cold than non-pigmented (hyaline) organisms. The pigment also protects against hydrolytic enzymes produced by environmental bacteria. Fungi produce different forms of melanin, although those based on DOPA (3,4-dihydroxyphenylalanine) or pentaketides are the most common. It is also apparent that fungi that do not appear visibly melanized may also contain melanin. The significance of fungal melanonychia is, therefore, that it represents a form of onychomycosis in which the organisms are likely to be more resistant to both host or therapeutic mechanisms.

In *Candida* infections of the nail there is often a greenish discoloration at the lateral margin and near the nail fold. This is particularly prominent in paronychia or where there is extensive onycholysis. The pigment is confined to the undersurface of the nail where there is onycholysis and can be removed by scraping the area. *Serratia marcescens* was responsible for nails in a patient with pseudochromhidrosis which was cured with oral cefcapene and topical naldixacin [226]. In paronychia the pigment may involve the upper surface of the nail plate. In most cases this is due to the presence of *Pseudomonas* species, but it is not clear whether this is a result of organisms within the nail plate or whether diffusible pigment is present. It is often difficult to exclude or prove in these cases whether gram-negative bacteria are present as well.

In most cases *Pseudomonas* species can colonize any area of the nail where there is onycholysis as well as the nail fold. The pigmentation that follows this colonization varies both with the species involved and with the composition of pigments produced. The colors vary correspondingly from a light green to dark green-black. *Pseudomonas* species produce a number of different diffusible pigments such as pyocyanin (dark green) and fluorescein (yellow-green). These are soluble in water, the former in chloroform as well [227]. This discoloration may involve the entire nail plate or simply part of it. Green striped nails may result from repeated episodes of bacterial infection with deposition of organisms and pigment during each episode [228]. Some help in the diagnosis can be obtained by soaking nail fragments in water or chloroform. If these turn green it is likely that *Pseudomonas* has been or is still present and this is the most likely reason for the deposition of pigment in the nail. Black discoloration of the nails due to *Proteus mirabilis* has been reported [229].

Pigmentation of the nail bed has been reported in pinta; secondary syphilis may present with chromonychia (Chapter 13).

Nail pigmentation secondary to fungi and possibly also to bacteria such as *Pseudomonas* spp. and *Proteus* spp. is usually readily identified also in histological nail sections. The nail plate exhibits a diffuse yellowish to brown discoloration that stands out in hematoxylin and eosin stain and more clearly in PAS stains.

2) Effects of systemic drugs and chemicals causes (see Chapter 16).
3) Longitudinal melanonychia (see Appendix).
4) Congenital and inherited disease (see Chapter 9).
5) Leukonychia.
6) Erythronychia.
7) Acral pigmentation.

**Leukonychia** (see also Appendix)

White nails are the most common chromatic abnormality of the nail and these can be divided into three main types: true leukonychia, in which nail plate involvement originates in the matrix; apparent leukonychia, with involvement of the subungual tissue; and pseudoleukonychia (Box 2.1).

In true leukonychia resulting from a structural modification of the nail fabric itself, the nail appears opaque and white in color owing to the diffraction of light in parakeratotic cells; with polarized light, the nail structure appears disrupted because of disorganization of the keratin fibrils. The leukonychia may be complete, total leukonychia (rare), or incomplete, subtotal leukonychia. These forms can be temporary or permanent depending on the etiology. Partial forms are divided into punctate leukonychia, which is common, transverse leukonychia, relatively common, and distal leukonychia, which is very rare.

Apparent leukonychia of a translucent nail plate, sometimes called leukopathia [18], can be further subdivided into a white appearance of the nail due to: (i) underlying onycholysis and subungual hyperkeratosis; (ii) modification of the subungual tissue giving rise, for example, to an apparent macrolunula.

The term pseudoleukonychia is used when the matrix is not responsible for the nail plate alteration, for example in onychomycosis (Fig. 2.47). Granulations of nail keratin resulting from nail enamel (Fig. 2.45a) look whitish, as does psoriasis. A transverse strip on the left fingernail was noted 1 h after a drop of a 2-ethyl cyanoacrylate glue was placed on it [230].

A different classification of leukonychia according to the location of the defect has also been suggested by Grossman and Scher [231], who give another meaning to some of the terms we are using.
True leukonychia

Total leukonychia

In this rare condition the nail may be milky, chalky, bluish, ivory, or porcelain white in color (Fig. 2.48a). The opacity of the whiteness varies. When it is faintly opaque, it may be possible to see transverse streaks of leukonychia in a nail with total leukonychia. Involvement of the longitudinal half of the nail plate has been described in a patient presenting total leukonychia in some other digits. Accelerated nail growth is associated with total leukonychia. Among congenital leukonychias, Kates et al. [232] presented the pedigree of a family with 28 affected members. Bart–Pumphrey syndrome [233] is an autosomal dominant disorder that demonstrates leukonychia, often associated with koilonychia, palmoplantar keratoderma, and sensorineural hearing loss, and is caused by a defect in the gene encoding connexin 26. Le Corre et al. [234] described a

Box 2.1 Classification of leukonychia (see appropriate chapters)

<table>
<thead>
<tr>
<th>Congenital and/or hereditary</th>
</tr>
</thead>
<tbody>
<tr>
<td>● Isolated or associated with other conditions (see Table 9.10)</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Acquired</th>
</tr>
</thead>
<tbody>
<tr>
<td>True leukonychia</td>
</tr>
<tr>
<td>● Alkaline metabolic disease</td>
</tr>
<tr>
<td>● Acute rejection of renal allograft</td>
</tr>
<tr>
<td>● Altitude leukonychia</td>
</tr>
<tr>
<td>● Alopecia areata</td>
</tr>
<tr>
<td>● Autonomic leukonychia</td>
</tr>
<tr>
<td>● Breast cancer</td>
</tr>
<tr>
<td>● Cachectic state</td>
</tr>
<tr>
<td>● Carcinoid tumors of the bronchus</td>
</tr>
<tr>
<td>● Cardiac insufficiency</td>
</tr>
<tr>
<td>● Crow–Fukase syndrome (POEMS)</td>
</tr>
<tr>
<td>● Cytotoxic and other drugs (emetine, pilocarpine, sulfonamide, cortisone, quinacrine, trazodone; see Chapters 16 and 17)</td>
</tr>
<tr>
<td>● Dyshidrosis</td>
</tr>
<tr>
<td>● Endemic typhus</td>
</tr>
<tr>
<td>● Erythema multiforme</td>
</tr>
<tr>
<td>● Exfoliative dermatitis</td>
</tr>
<tr>
<td>● Fasting periods in orthodox Jews</td>
</tr>
<tr>
<td>● Fracture</td>
</tr>
<tr>
<td>● Gout</td>
</tr>
<tr>
<td>● Hodgkin disease</td>
</tr>
<tr>
<td>● Hyperalbuminemia</td>
</tr>
<tr>
<td>● Hypocalcemia</td>
</tr>
<tr>
<td>● Immunohemolytic anemia</td>
</tr>
<tr>
<td>● Infectious diseases and infectious fevers</td>
</tr>
<tr>
<td>● Intraabdominal malignancies</td>
</tr>
<tr>
<td>● Kawasaki syndrome</td>
</tr>
<tr>
<td>● Kidney transplant</td>
</tr>
<tr>
<td>● Leukoonycholysis paradentotica</td>
</tr>
<tr>
<td>● Leprosy</td>
</tr>
<tr>
<td>● Lichen planopilaris</td>
</tr>
<tr>
<td>● Malaria</td>
</tr>
<tr>
<td>● Malnutrition and myxedema</td>
</tr>
<tr>
<td>● Menstrual cycle</td>
</tr>
<tr>
<td>● Myocardial infarction</td>
</tr>
<tr>
<td>● Nitric acid, nitrite solution</td>
</tr>
<tr>
<td>● Occupational</td>
</tr>
<tr>
<td>● Parasitic infections</td>
</tr>
<tr>
<td>● Pellagra</td>
</tr>
<tr>
<td>● Peripheral neuropathy</td>
</tr>
<tr>
<td>● Pneumonia</td>
</tr>
<tr>
<td>● Poisoning (antimony, arsenic, carbon monoxide, fluoride, lead, thallium; see Chapter 16)</td>
</tr>
<tr>
<td>● Protein deficiency</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Apparent leukonychia</th>
</tr>
</thead>
<tbody>
<tr>
<td>● Anemia</td>
</tr>
<tr>
<td>● Cancer chemotherapeutic agents (Chapter 17)</td>
</tr>
<tr>
<td>● Cirrhosis</td>
</tr>
<tr>
<td>● Electron beam</td>
</tr>
<tr>
<td>● Fly–tyer’s finger</td>
</tr>
<tr>
<td>● Half-and-half nail (renal diseases, androgen, 5-fluorouracil) and distal crescent pigmentation</td>
</tr>
<tr>
<td>● Kawasaki disease</td>
</tr>
<tr>
<td>● Leprosy</td>
</tr>
<tr>
<td>● Muehrcke’s lines with normal albuminemia or hypoalbuminemia</td>
</tr>
<tr>
<td>● Ulcerative colitis</td>
</tr>
<tr>
<td>● Peptic ulcer disease and cholelithiasis</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Pseudoleukonychia</th>
</tr>
</thead>
<tbody>
<tr>
<td>● Onychomycosis</td>
</tr>
<tr>
<td>● Keratin granulation (nail varnish, base coat)</td>
</tr>
<tr>
<td>● Cyanoacrylate glue</td>
</tr>
</tbody>
</table>
single family which demonstrated leukonychia totalis, acanthosis nigricans-like lesions, and hair dysplasia. Genetic linkage indicated that the gene defect underlying the leukonychia in the family studied by Norgett et al. [235] resides on chromosome 12q13. As the type II keratins (cytokeratins and hard keratins) map within this chromosomal interval, it is possible that a mutation in one of these keratin genes may be a cause of the hereditary leukonychia. Sporadic congenital leukonychia with partial phenotype expression has been reported in a 12-year-old boy whose nail color was consistently white in his second, third, and fourth fingers on both hands since birth [236]. The nails of the thumb and fifth finger on both the right and left hand alternated in color such that at times the thumb would be white and the fifth finger pink and vice versa. Other well-established syndromes are included in Chapter 9.

Acquired leukonychias may be exogenous or endogenous. Acquired leukonychia totalis has been seen associated with reflex sympathetic dystrophy [237]. Acquired leukonychia without other systemic findings has rarely been reported [238] as well as autonomic leukonychia associated with cold sweaty hands and pallor of the fingers unrelated to ambient or body dysfunction [239].

**Subtotal leukonychia**

In this form, there is a pink arc about 2–4 mm wide distal to the white area. This can be explained by the fact that the nucleated cells in the distal area mature, lose their keratohyalin granules, and then produce healthy keratin several weeks after they have been formed. Subtotal leukonychia as well as transverse leukonychia may be a phase of total leukonychia based on the occurrence of both in different members of one family and the simultaneous occurrence in one person. In addition, either type may be found separately in some persons at different times [240]. These observations strongly suggest that the two conditions are probably variable expressions of the same genetic defects [236]. Albright and Wheeler [241] saw also total or partial leukonychia in a single family. In the family reported by Bettoli and Tosti [242], in contrast, all the patients affected by total leukonychia at birth experienced a gradual improvement of the nail discoloration during the course of life. A white discoloration was observed in all fingernails in a 16-year-old male patient together with linear atrophyderma of Moulin [243].

**Transverse leukonychia**

One or several nails exhibit a band, usually transverse, 1 or 2 mm wide, and often occurring at the same site in each nail resulting, for example, from acute arsenic toxicity (Mees’ lines), trauma, repeated microtrauma resulting from lack of trimming and impinging on the distal part of the shoe [244] (Fig. 2.48b), acute rejection of renal allograft [245], systemic chemotherapy [246], systemic infection [247], severe hypocalcemia [248], and pleural empyema [249]. This condition may be inherited. Mahler

---

**Figure 2.47** Pseudoleukonychia due to *Scopulariopsis brevicaulis*.

**Figure 2.48** (a) Total leukonychia. (b) Transverse leukonychia due to repeated microtrauma of the free edge. (c) Leukonychia variegata.
et al. [250] reported on a congenital type involving only the entire great toenail and half of the second toe of both feet. “Everest nails” describe transverse white bands which were seen in a man who spent more than 11 weeks climbing on Mount Everest. These bands were found on the nail plates of all of the fingers and toes. The width of the bands corresponded to the time he spent at extremely high altitude. The authors speculated that the white bands may have been caused by altitude-related hypoxia and catabolic stress [114]. Burtscher and Likar [251] described two individuals who developed transverse leukonychia after ingestion of acetazolamide and naproxen during exposure to a high-altitude environment. Maino and Stashower [252] described transverse leukonychia in a patient with anxiety, who would bite, pick, and tap the nails against flat surfaces. The leukonychia resolved after he stopped tapping the nails. Electron beam irradiation [253] may produce transverse leukonychia.

**Isolated distal leukonychia**
This condition is seldom observed.

**Punctate leukonychia**
In this type, white spots 1–3 mm in diameter occur singly or in groups; only rarely do they occur on toenails. Their appearance is usually due to repeated minor trauma to the matrix. The evolution of the spots is variable; appearing generally on contact with the cuticle, they grow distally with the nail but about half of them disappear in the course of their migration towards the free edge. This proves that parakeratotic cells are capable of maturing and losing their keratohyalin granules to produce keratin, even though they have been without vascularization for many months. Some white spots enlarge, whereas others appear at a distance from the lunula, suggesting that the nail bed is participating by incorporating groups of nucleated cells into the nail [254]. A similar process could explain the exclusively distal leukonychia which is occasionally seen [255]. A local or general fault in normal keratinization is not the only cause of punctate leukonychia. Infiltration of air, which is known to occur in cutaneous parakeratoses, may also play a part.

**Leukonychia variegata**
Leukonychia variegata [18] consists of white irregular transverse thread-like streaks (Fig. 2.48d).

**Longitudinal leukonychia**
Longitudinal leukonychia is a typical example of a localized metaplasia [18]. It is characterized by a permanent grayish white longitudinal streak, 1 mm broad, below the nail plate (Fig. 2.49). Histologically there is a mound of horny cells causing the white discoloration due to a lack of transparency resulting in alteration in light diffraction.

Early stages of longitudinal splits and ridges of the nail may appear as white streaks. Two stripes in one nail may occur. Occasionally, two or three nails may be affected in the same person [256]. Higashi et al. [257] described longitudinal leukonychia resulting from parakeratotic hyperplasia of the nail bed epidermis, with or without abnormal keratinization of the deeper cells of the nail plate, because of nevoid matrix changes.

It can represent Darier disease [60], which is definitely too restrictive, Hailey–Hailey disease, and tuberous sclerosis complex. Moulin et al. [258] have reported epidermal hamartoma presenting as double longitudinal pachyleukonychia restricted to fingernails. Onychopapilloma has been described as a solitary band of longitudinal leukonychia [259] that has also been observed in Bowen disease.

A medial longitudinal half-and-half true leukonychia has been reported in a 45-year-old patient presenting a hallux valgus [260].

**Apparent leukonychia**
**Terry’s nail**
Terry [261] was the first to describe white opacity of the nails in patients with cirrhosis (Fig. 2.50). In the majority of cases the nails are of an opaque white color, obscuring the lunula. This discoloration, which stops suddenly 1–2 mm from the distal edge of the nail, leaves a pink to brown area 0.5–3.0 mm wide not obscured by venous congestion and corresponding to the onychodermal band. It lies parallel to the distal part of the nail bed and may be irregular. The condition involves all nails uniformly. Revised definition and new correlations on
Terry’s nails have been advocated by Holzberg and Walker [262]. They found that a distal brown band was four times more frequent than the normal pink band as described by Terry. The proximal nail beds of a quarter of the patients were light pink, rather than white with a ground-glass opacity. The nail abnormality is associated with cirrhosis, and demonstrated in associations with chronic congestive heart failure, adult-onset diabetes mellitus, and age. The biochemical abnormalities that were associated with Terry’s nails may be related to the underlying disease and not causally related to the nail disorder. The pathological findings from all three patients who underwent biopsy demonstrated an underlying change in vascularity. Telangiectasias were found in the dermis of the band. For a more complete discussion of Terry’s nails, see Chapter 15. Morey and Burke’s nail [263] is a variation of Terry’s nail. The authors reported four cases in which the whitening of the nail extended to the central segment with a curved frontal edge; one of the cases had identical changes in the toes.

Uremic half-and-half Lindsay’s nail [264] (ongle équisegmenté hyperazotémique [265])

In this disorder, the nail consists of two parts separated more or less transversely by a well-defined line; the proximal area is dull white, resembling ground glass and obscuring the lunula; the distal area is pink, reddish, or brown, and occupies between 20% and 60% of the total length of the nail (average 33%) (Fig. 2.51). In typical cases diagnosis presents no difficulty, but in Terry’s nails the pink distal area may occupy up to 50% of the length of the nail, in which case the two types of nail may be confused. Half-and-half nail can display a normal translucent proximal half portion with a distal brown nail bed arc [266]. Sometimes the distinctly abnormal onychodermal band extends approximately 20–25% from the distal portion of the fingernail as a distal crescent of pigmentation with pigment throughout the brown arc of the nail plate [266]. Half-and-half nail is found in approximately 40% of patients with chronic kidney disease and is a relatively specific marker of its end stage. A similar type of nail change has also been described in Cash disease, Kawasaki disease, Behçet disease, cirrhosis, zinc deficiency, pellagra, and HIV infection [267]. Half-and-half nails have occurred after chemotherapy, and in a patient with breast cancer after androgen use; this patient had not required chemotherapy for her tumor [268]. For a more complete discussion of the uremic half-and-half nail, see Chapter 15.

Muehrcke’s paired, narrow white bands [269]

These bands, which are parallel to the lunula, are separated from one another, and from the lunula, by strips of pink nail (Fig. 2.52). They disappear when the serum
albumin level returns to normal and reappear if it falls again. It is possible that hypoalbuminemia produces edema of the connective tissue in front of the lunula just below the epidermis of the nail bed, changing the compact arrangement of the collagen in this area into a looser texture, resembling the structure of the lunula; hence the whitish color. The correlation between the presence or disappearance of the white bands and the amount of serum albumin seems to confirm this hypothesis. However, white fingernails preceded by multiple transverse white bands have been reported with normal serum albumin levels. Cytotoxic drugs may produce Muehrcke’s bands. Unilateral Muehrcke’s lines may develop after trauma [270].

**Neapolitan nail**
Nail changes similar to those reported by Terry, Lindsay, and Muehrcke have been termed “Neapolitan nail” [271]; they are probably simply an age-related phenomenon. Apparent leukonychia may be preceded by multiple transverse white bands [272]. They disappear when blanching the fingertips. We have observed an identical case with vascular impairment. The white bands transformed gradually into total apparent leukonychia each winter and reappeared each summer. For a more complete discussion of Muehrcke’s bands, see Chapter 15.

**Longitudinal apparent leukonychia**
This was seen in a patient presenting with a subungual epidermoid inclusion [273].

**Anemia**
Anemia produces a pallor of the nail bed.

**Dermatological forms of leukonychia**
In psoriasis the nail may be affected by true leukonychia, due to involvement of the matrix, and apparent leukonychia, due to onycholysis, and/or to parakeratosis deposits in the nail bed. The parakeratotic cells filling the pits of the dorsum of the nail usually disappear quickly when they come from beneath the proximal nail fold. It happens that these cells adhere to each other, producing the superficial white friable quality of the nail plate. One of the earliest signs of leprosy is an apparent macrolunula, which may become total in dystrophic leprosy. Leukonychia may also occur in other acquired dermatoses, such as alopecia areata, dyshidrosis, or inherited conditions (Chapter 9).

**Erythronychia**

**Longitudinal erythronychia**
A red longitudinal streak may be found in the nail plate in a range of disorders and patterns. Longitudinal erythronychia can be divided into localized longitudinal erythronychia, which involves a single nail unit, and polydactylous longitudinal erythronychia, in which multiple nail units are involved [274]. Localized longitudinal erythronychia is caused by local processes and tumors, most commonly an onychopapilloma. Benign causes of localized longitudinal erythronychia include a verruca, warty dyskeratoma, and glomus tumor. Malignancies including squamous cell carcinoma in situ, melanoma in situ, and basal cell carcinoma can also present in this fashion. When multiple nail units are affected, a systemic cause or inflammatory disorder is most likely. The differential diagnosis for polydactylous longitudinal erythronychia includes Darier disease, lichen planus, systemic amyloidosis, graft-versus-host disease, and celiac disease [275].

De Berker et al. [276] describe a potential mechanism to explain the development of longitudinal erythronychia. An abnormal process creates a defect in matrix function, which results in a longitudinal groove formed in the nail plate, which is thinned. The thinned nail plate allows easier visualization of the underlying nail bed vasculature. Additionally, the normal nail compresses the nail bed and highlights the engorged nail bed trapped in the groove [277]. Idiopathic polydactylous longitudinal erythronychia is seen in the absence of an associated systemic or dermatological condition, and can be associated with painful nails and nail fragility [277].

**Red lunula**
Red lunula (Fig. 2.53) can be observed in patients with several cutaneous or systemic disorders [278] or it may be idiopathic. The sharply circumscribed erythema of the lunulae can affect all fingernails and toenails or only some fingernails, especially the thumbs. Dark erythema may diffuse onto the proximal pink nail bed or a narrow white band may be present at the distal lunulae. The erythema of the fingernail lunulae migrated distally in a unique case of severe alopecia areata [279]. The erythema disappears under pressure to the nail.

**Figure 2.53** Red lunulae with longitudinal erythronychia.
plate. The lunular erythema usually fades slowly even without therapy. The pathogenesis of red lunula remains undetermined. Biopsy specimens taken from the red lunula of a thumb revealed neither an increased number nor increased size of capillaries [280] (see Appendix for the differential diagnosis).

**Acral pigmentation**

Acral pigmentation includes different conditions. Some are observed in newborns; others may be a predominant feature in uncommon disorders.

Acromelanosis is characterized by increased pigmentation on the acral areas of the fingers and toes. It is mostly seen in newborns or during the first year of life. Periungual hyperpigmentation is a physiological melanic pigmentation in the early months of life.

**Acromelanosis progressiva**

This condition is viewed as the epidermal counterpart to pigmentary disorders composed of dermal melanocytes and epidermal melanocytosis since birth. Blue-black, irregular, dot-like macules appeared on the periungual areas of the fingers of a patient’s right hand [281].

**Acropigmentation (Spitzen pigment)**

Restricted to the fingers and toes, this pigmentary condition is characterized by brown undefined discoloration that diminishes gradually in intensity in the fifth year of life [282].

**Symmetrical acropigmentation of Dohi** *(dyschromatosis symmetrica hereditaria)*

This appears in early childhood symmetrically on the dorsa of the hands and feet and periungual areas as ongulated freckle-like lesions that join at the margins to form a reticulate pattern. It is inherited as an autosomal dominant trait. The disease is believed to be relatively common in Japan. The eruption slowly extends proximally and may affect the sides of the neck and the supravacular region.

**Reticulate acral pigmentation of Kitamura** *(acropigmentation reticularis)*

This disorder is rather similar to symmetrical reticulate pigmentation of Dohi. It involves the extensor surfaces of the hands and feet and periungual areas as freckle-like, reticulate atrophic macules. However, there are no leukodermic macules and the pigmented lesions are clearly atrophic clinically and histologically. The hyperpigmentation is due to an increased number of active melanocytes and to increased transfer of melanosomes to surrounding keratinocytes. The disease is inherited as an autosomal dominant trait. Acropigmentation of

![Figure 2.54 Ethnic pigmentation. Courtesy A. Taieb.](image1)

![Figure 2.55 Trichrome vitiligo. (a) First stage. (b) Final stage. Courtesy of N. Di Chiaccio.](image2)
Kitamura and acropigmentation of Dohi do not show incontinence of pigment in biopsy specimens [283].

**Universal acquired melanosis**

A progressive dark brown pigmentation of the face and extremities with accentuation in the periungual area has been observed in a 15-day-old white Mexican boy. By the age of 3, the child had become universally black [284].

**Ethnic nail pigmentation**

This rare condition has been observed in Burkina Faso. Present at birth, it does not tend to regress (Fig. 2.54).

**Nail trichrome vitiligo**

This exceptional appearance is a transitional pigmentary state with three stages of color: brown, tan, and white in the same patient [285] (Fig. 2.55a,b).

**Nail bed pigmentation**

Melanocytes of the nail bed may be activated in inflammatory disorders such as Hallopeau disease (Fig. 2.56).

---

**References**

18. Basset H. (1962). Trois formes génotypiques d’ongles courts, le pouce en raquette, les doigt en raquette, les...


Physical Signs


Introduction

Photography should be considered the most at-hand non-invasive imaging technology. Clinical photographs are useful as long as the quality is good and they have been taken under standardized conditions (e.g., light, position, backdrop, and distance). In this regard, the advent of digital photography has greatly simplified the task, allowing physicians (non-professional photographers) to take good quality images of their patients. In fact, digitalization has increased the use of images for patient care, education, and research.

With regard to nail photography, many concepts are shared with medical photography, but there are some special considerations that must be kept in mind.

Why do we need dermatological photography?

Photography of the nails should take account of the following [1].

- Photographs should be part of the medical records since a good image is worth a thousand words. There are aspects that are very difficult to explain without the use of appropriate images. Also, incorporation of visual data into a patient’s medical record is invaluable for future reference and indispensable for others (nurses, pathologists, etc.) in charge of a patient’s care who have not had direct contact with the patient. In a survey conducted on 1000 dermatologists, 89% agreed that the use of digital photography enhanced patient care [2].
- Photographs are an educational tool (for ourselves, to teach others, for publication purposes). Clinical photographs have an important role in education specifically to show classical presentations, rare or acute diseases, and teaching large audiences [3].
- Clinical photographs are useful in getting a second opinion.
- They are helpful to show the effects of treatment to the patient and for patient counseling.
- Photograph can be used to document changes in skin pathology over time (tracking of disease progression).
- They help to determine disease patterns.
- Photograph post-processing allows images to be enhanced and gives additional valuable information.
- Photography can help to make consultation by remote experts (teledermatology) viable and valid.

CHAPTER MENU

<table>
<thead>
<tr>
<th>Introduction, 105</th>
<th>Depth of field, 107</th>
</tr>
</thead>
<tbody>
<tr>
<td>Why do we need dermatological photography?, 105</td>
<td>White balance, 107</td>
</tr>
<tr>
<td>When: respect and consent form, 106</td>
<td>Resolution: camera sensor size versus pixel myth, 108</td>
</tr>
<tr>
<td>Which camera? Technical aspects, 106</td>
<td>Photographing nails, 108</td>
</tr>
<tr>
<td>Cameras, 106</td>
<td>Hand position: consistency, 108</td>
</tr>
<tr>
<td>Light/flash, 106</td>
<td>Foot position, 108</td>
</tr>
<tr>
<td>Distance, 107</td>
<td>Hand location: backdrop, 108</td>
</tr>
<tr>
<td>Lenses: zoom versus fixed focal or prime lenses, 107</td>
<td>Intraoperative photography, 109</td>
</tr>
<tr>
<td>Cross-polarized photography and transmission mode photography, 110</td>
<td></td>
</tr>
<tr>
<td>Three-dimensional photography, 110</td>
<td></td>
</tr>
<tr>
<td>Picture format, 110</td>
<td></td>
</tr>
<tr>
<td>Photographic measuring scale, 111</td>
<td></td>
</tr>
<tr>
<td>Post processing/computer-aided analysis, 111</td>
<td></td>
</tr>
<tr>
<td>Where and how to store images: medical imaging software, 111</td>
<td></td>
</tr>
<tr>
<td>Legal aspects, 111</td>
<td></td>
</tr>
</tbody>
</table>
When: respect and consent form

The first condition for taking a picture is to have the patient’s consent. Taking a picture of a patient – even if it is a localized body part, as is the case in nail photography – presupposes a respectful attitude towards the patient. Clinical pictures should be used exclusively for medical purposes. The presence of recognizable features gives an additional burden of participation as the patient can be recognized by him/herself or others even by photographs of their fingers. Respect towards patient confidentiality is essential and consent is an absolute requirement, both verbal and written. An informed medical consent provides a legal and ethical framework within which the patient–physician relationship can better operate [4]. Never forget that the physician–patient relationship is fiduciary. This means that the patient believes and trusts that the physician will apply his or her professional expertise in the patient’s interest and benefit and would do nothing to harm the patient [5]. As images are used outside of individual care (for education, a second opinion, etc.) privacy can be a concern for many patients. The care and dignity of the patient should always outweigh any other interests. Consent forms will be different from one center to another and they will need to be approved by the local ethics committee. They should nonetheless include a clear understanding of the purpose of the photography, the risk of failure to consent to it, and an explanation of the security and confidentiality of the photographs [4]. Organizations can choose to identify photographic consents in any of three categories (education, publication, and documentation) [6]. For dermatological purposes, an all-inclusive consent simplifies the process. For some authors, consent is unnecessary when non-identifiable digital images are used for educational purposes [7]. When photographs are used for educational purposes, de-identification can help but is not always absolute.

Digital images are easily manipulated. Altering, faking, or staging are unethical conducts. This should not be confused with post-image processing, which can enhance features, improve image quality, and offer further information on the medical condition.

In general, patients have a favorable impression of medical photography, especially when non-sensitive body areas are photographed [8]; to avoid the violation of legal requirements hospital-owned cameras are highly preferable to personally owned cameras or smartphones [9], although some studies have found that most patients were comfortable with dermatologists using personal smartphones for clinical photographs [10]. Nails are especially non-sensitive areas to photograph, and therefore their imaging should not generate any ethical or legal issues. Nevertheless, it is important to remove rings or bracelets whenever possible in order to avoid leaving any recognizable elements and allow a better standardization of the image. Tattoos pose an identification risk that should not be overlooked. Different countries have different regulations in relation to medical photography and some have guidelines for best practices. There are racial, ethnic, religious, age, gender, and cultural aspects that might generate discomfort with the use of clinical photography and should be addressed before photographing a patient. The patient’s consent document should address these issues in a satisfactory way.

Which camera? Technical aspects

Cameras

Choosing a digital camera can become a difficult task considering the huge selection available on the market; nowadays, smartphones and tablets need to be included in this long list as their cameras are continuously improving. It is essential to have good equipment: this will be an investment that will translate to better images for medical records. Although this chapter cannot replace a photography manual, certain notions are worth mentioning in regard to ideal equipment. Table 3.1 shows a summary of the most common equipment that is available. Analog cameras will not be discussed in this chapter as they are not easily available and the cost of film and film processing make them impractical for everyday use.

Light/flash

Using a flash standardizes light, as it has a constant power and color temperature (5550 K), while ambient light is inconsistent because it changes continuously not only according to the hour of the day but also according to the location, type, and intensity of artificial light used. A variety of twin-light and externally mounted flash units are available. A ring-light configuration can work nicely as well as systems that can be integrated with a lens metering system [11]. Upper range cameras may have several individual flash lamps that can be adjusted. Fixed flashes are not desirable because the light hits the center of the subject, leaving a “burn” effect. Built-in flashes need to be adjusted because in nail photography the distance to the subject is usually short. To reduce flash brightness, diffusers can be of great help. For built-in flashes one trick to lower brightness is to cover the flash with white paper or tape. The resulting pictures are excellent and highly repeatable series are possible.

If space permits it, studio lighting systems offer the best solution. They should be ideally used with distancing systems and patient positioning mats.
Nail Photography

Distance

The distance from the camera and the subject should always be the same. Some new camera models have integrated ranging lights to assure perfect camera-to-subject distance for every picture, or laser lights to verify the correct distance.

Lenses: zoom versus fixed focal or prime lenses

Macrolenses are ideal for close-up photography, with a “flat-field” focusing band that is ideal for a subject in one single plane, which is why they work well in nail photography. As opposed to zoom lenses, prime lenses with a 50–60-mm (35-mm equivalent) focal length are an excellent option for nail photography [12].

Depth of field

Depth of field (DOF), also called the focus range or effective focus range, is the distance between the closest and farthest objects in a scene that appear sharp in an image. If it is necessary to “isolate” subjects from the background, use a shallow DOF (emphasize the subject and de-emphasize the background). DOF is dependent upon three factors: aperture value, focal length, and subject distance. In dermatology there is a tendency to prefer the whole subject in focus; therefore, the use of narrow apertures is mandatory (greater depth of field) [13]. When each of the other two variables is fixed, setting a larger F-stop number (which actually means a smaller aperture opening) will result in a larger DOF [14]. The smaller aperture will need to be compensated by increasing the sensor sensitivity (higher ISO, which translates into a reduction of image quality) and/or by having a brighter environment (more light/flash). (A high ISO means an increased sensitivity to light but more “noise” or “grain”; a low ISO means a lower sensitivity to light and a higher quality image, but insufficient light will need to be compensated with a flash, by lowering the shutter speed with subsequent risk of blurring the image, or by increasing the aperture at the risk of changing the DOF).

Plenoptic cameras (light-field cameras) are already available. An array of microlenses between the front lens and the sensor capture information about the light field emanating from different points and directions (conventional cameras only capture intensity). Post processing of such an image can be later reconstructed into a three- or two-dimensional image The result is an all-focused combined image composed of multiple smaller individually DOF-manipulated images [15].

White balance

By adjusting white balance one can correct unrealistic color casts. When taking a picture, for color accuracy the white in the real image should be the same as the white shown in the photograph. Different light sources have different color temperatures, which changes the way

<table>
<thead>
<tr>
<th>Name of camera</th>
<th>Advantages</th>
<th>Disadvantages</th>
</tr>
</thead>
<tbody>
<tr>
<td>Compact camera (point and shoot)</td>
<td>Very small, Inexpensive, Light, Easy to use, LCD</td>
<td>Fixed lenses, Small storage capacity, Mass depth of field (?)</td>
</tr>
<tr>
<td>Bridge camera, or compact with large zoom</td>
<td>Small, Quality of image: good to excellent, Manual control, Macrolenses, LCD, Ring flash adaptable</td>
<td>No OVF (except some models, e.g. Fujifilm XT1) (optical vs electronic viewfinders), As expensive as SLR</td>
</tr>
<tr>
<td>Mirrorless camera (interchangeable-lens mirrorless)</td>
<td>Interchangeable lenses, Relatively small</td>
<td></td>
</tr>
<tr>
<td>Reflex digital camera or SLR</td>
<td>Measurements through lenses, Flash adjustment, OVF, Maximum quality images, Interchangeable lenses, Ring flash</td>
<td>Bigger, Heavier, More expensive</td>
</tr>
</tbody>
</table>

LCD, liquid crystal display; OVF, optical viewfinder; SLR, single-lens reflex.

| Table 3.1 Digital camera types. |
white color is rendered in the photo. By adjusting the camera’s white balance, colors can have a more realistic feeling of higher accuracy. White balance is a feature that can be set in automatic or adjusted manually. A more precise manner to adjust the camera to the light source is using a color chart which consists of a cardboard-framed arrangement of painted samples. A picture of this chart is later compared with the original chart and adjustments can be made accordingly, either by post processing or on the camera for future use (as long as the light conditions are maintained) [16].

Resolution: camera sensor size versus pixel myth

It is not only the number of pixels that matters. Camera sensor (CS) size is even more important. The CS is the photosensitive area that captures light and converts it into a digital image. A pixel is the smallest unit of information that makes up a picture. The size of the sensor divided by the number of pixels determines the size of each pixel: the larger the pixel, the higher the quality of the image. For an equal number of megapixels, the best images will be from the camera with the larger sensor.

Photographing nails

Hand position: consistency

There are no standard guidelines for imaging nails. Ideally, all nails should be visualized in a single frame; however, flexing the digits might not be a simple task for some patients. To overcome these difficulties, several other postures have been proposed. Ashique and Kaliyadan [17] suggest taking two images: one of all the fingernails excluding the thumbs and a second of only the thumbs. Later, a panel/collage can be created [17] (Fig. 3.1). This proposal has the disadvantage of requiring the creation of a postprocessing collage but the advantage is in the ease of positioning the patient, especially for those with reduced joint mobility. If such positioning is chosen, it is helpful to have a chart with the finger positions available in order to maintain consistency each time a photograph is taken over different time periods. Furthermore, standardization of images is easier than with any other position [18]. Gupta and Gupta [19] proposed placing the hands one over the other as this allows all eight fingers to be seen at once; however, this has the disadvantage that the hands are placed at different levels, leaving one hand slightly out of focus [20] (Fig. 3.2). For patients without joint involvement, Inamadar and Palit’s [21] all-inclusive nail position seems ideal (Fig. 3.3). Consistent positioning of the hand/foot between the two measurements is a requirement for future comparisons.

Foot position

Positioning the feet is much simpler (Fig. 3.4). This can be done either by placing a backdrop on the floor or by having the patient lie down with the backdrop placed behind 1 m away; the photograph is taken by placing the camera close to the patient’s knees. Keeping the feet still is key to avoiding blur and thus to getting a sharp image; this can be more easily achieved with the patient’s feet on the floor above a backdrop.

Hand location: backdrop

Backdrops are essential in good photography. They must be used as follows.

- Unify the background. This avoids distracting and non-related images in the background.
- Facilitate standardization. The use of backdrops facilitates comparing clinical images taken at different times.

![Figure 3.1](image-url) Ashique and Kaliyadin’s proposed hand position, in which all eight fingernails excluding the thumb are in one picture by placing the hand flat (a). The thumbs are then laid flat for the second picture (b). A panel with both images is then created. Picture taken with a Canfield® TwinFlash RL Clinical Camera with a flat light blue paper backdrop.
Avoid “forcing” the lens (set in macro) to select between focusing on the background or on the subject. A black backdrop facilitates postproduction combination of two images taken at different points in time.

- The most common backdrops are: (i) black, non-glossy velvet backdrops; (ii) medium-toned cloth or paper backdrops in light blue or neutral grey. Black absorbs excess light without reflecting it. A black backdrop helps obtain better image contrast, thus focusing attention on the subject. In PowerPoint (PPT) presentations, black background images blend nicely with the standard black background provided by PPT. On the other hand, a lighter backdrop could help avoid overexposing the photograph, given the existing high contrast among subject and backdrop; a problem that can be easily overcome by reading light only for the subject and not the backdrop. Finally, lighter colors are best for darker skin types.

- Position of the subject (nails) in relation to the backdrop. Ideally, one needs to maintain a distance between the subject and the backdrop, especially when light backdrops are used. This avoids default shadows that show up in the photograph (on the backdrop). The short depth of field of a macro lens combined with precisely targeted illumination of the object by a TTL flash (through-the-lens metering, non-manual flash) will artificially create a black background with a highly contrasted image [22]. Insufficient distance will record information on the background itself, giving an undesired effect. One possible problem is maintaining the hand or foot steady for the picture. In macrophotography, tremors result in photographs that are out of focus. Kaliyadan and Ashique [23] suggest resting the fingers on a tripod; they obtained good results with distances shorter than 1 m with a 100-mm macro lens zoomed out with the flash on. For feet, the task is simplified because the patient can lie down or sit with the legs stretched out on a bed while a backdrop is placed 1 m away. Others prefer placing the hands or feet directly on the backdrop to avoid movement (Fig. 3.5).

**Intraoperative photography**

Dermatological surgeons are more likely than other dermatologists to use photography. This is probably because of their desire to document the progress of their surgical cases [24]. García-Ramascó et al. [25] proposed the use of sterile underwater housing to protect the camera. These cases are heat sensitive and require cold sterilization such as hydrogen peroxide gas plasma. Before the operation,
the sterile case with the camera inside can be safely placed on the operating table and used as needed. These housings are commercially available for many digital cameras. The use of scialytic lights – lights that disperse or dispel shadows – provides very-high-intensity illumination, which results in more contrasted pictures. Ideally, it is better to use a central single point mode to adjust the exposure and autofocus in the center of the operating scene [26]. Other alternatives are high-resolution cameras mounted on camera arms fixed on the roof, placed on a tripod, or mounted on the head.

For those who can operate with a professional photographer on site, a focal length of 80–100 mm allows for a 70–80-cm distance from the operative field.

**Cross-polarized photography and transmission mode photography**

There are new cameras that come with a cross-polarized filter kit [27]. In reflection mode (reflection mode is standard flash photography in which the camera captures light reflected from the subject) a cross-polarized image allows one to see through the nail plate and evaluate the skin beneath it (nail bed) (Fig. 3.6).

In transmission mode a light source illuminates the finger(s) from below and an image of the light transmitted through the finger and nail is captured from above. In the latter mode a red color light source is preferable since it will undergo negligible tissue absorption and have higher transmission than other colors.

**Three-dimensional photography**

There are cameras capable of generating three-dimensional images. They use stereophotogrammetry technology, which uses three photographic images taken at different positions to estimate coordinate points; these are then reconstructed into one image through image stitching. They are preferable to two-dimensional photographs when evaluating nails and the surrounding skin because they allow physicians to reliably see both the side and the base of the fingernail–tissue interface. Three-dimensional images can also provide true surface area measurement. Unfortunately, commercial three-dimensional cameras have been specifically designed for photographing faces. The larger field of view inherent in commercial three-dimensional cameras generally precludes their use for nail studies.

**Picture format**

Always take pictures at maximum resolution, adjusting the camera to superfine mode. If your camera allows it, take images in .raw + .jpeg format. (A raw file is an image format in which data remain uncompressed and unprocessed. It is the equivalent to the negative in film photography; jpeg (Joint Photographic Experts Group) is a standard method of digital image compression that
results in a reduction in storage size to the detriment of image quality.) High-quality images will enable editing when necessary. Pictures can always be downgraded, never upgraded. For image sharpness, the ISO mode should be adjusted – the lower the better; it is best to keep this below the 100 range. Rasterized-based files (i.e. with a .tiff or .jpeg extension) require a resolution of at least 300 dpi (dots per inch) [28].

Photographic measuring scale

Digital rules provide a neater, more precise, and professional way to measure photograph lesions. Stickers should be avoided as they look untidy, they can be difficult to place in the correct area, and they are uncomfortable to remove. Digital rules avoid contacting the patient. The digital rulers are dragged onto the image from a layer in a ready-made .psd file, of which a number of sizes are available in the magnification ratios commonly used for close-up photography of lesions [29].

Post processing/computer-aided analysis

Standardization of a clinical image is essential to track improvement, stabilization, or worsening of skin conditions. This enables clinicians to observe such changes. A classic example is the before-and-after surgery sequence, but digitalization offers additional advantages. Automated image analysis gives an objective quantitative estimation of the therapeutic response. Digitalized mole evaluation is one such example of diagnosis of early changes that are detectable only when comparison of two standardized images is available [30]. RBX® technology (Canfield® Scientific) separates colors (red and brown components) to improve visualization of skin conditions. Postprocessing infrared filters enhance visualization of keratin (white) and vascular areas (black).

Where and how to store images: medical imaging software

DICOM (Digital Imaging and Communication in Medicine) is a standard for handling, storing, printing, and transmitting information in medical imaging. Each DICOM file includes administrative tags with the patient’s information and includes an image in .jpeg/tiff/raw format. Special Medical Images Organizer (MIO) software can convert files into DICOM format so they can then be sent to Picture Archiving and Communications Software (PACS).

PACS is a system of archiving and reporting electronic images that has become a substitute for the old way of manual filing, retrieving, and transporting of film jackets. The format for PACS image storage and transfer is DICOM [31].

Some authors have proposed barcode labeling systems to store clinical photographs [32].

Legal aspects

As digital images become easier to circulate, protection of a patient’s privacy is even more essential. Publishing without consent may expose the clinician to legal liability [33]. There are laws covering the use of personal images by third parties. Written consents are preferred over verbal consents and the written consent form should include those uses that are permitted (consultation, teaching, publication). Each institution should have its own all-inclusive consent form, thus saving time for both clinicians and patients. In regards to teaching, speakers should always remind their audience that photographing slides containing patient’s images is forbidden.

References


Chapter 4
Dermoscopy
Luc Thomas, Sébastien Debarbieux, and Amélie Boespflug

Department of Dermatology, Centre Hospitalier Lyon Sud; Lyon Cancer Research Center (Pr Puisieux); Lyon 1 Claude Bernard University, Lyon, France

Introduction

It might seem odd to suggest that dermoscopy is a way of “imaging” the nail unit since many authors consider that it belongs to the clinical examination of many conditions of skin and nails. Indeed, the quality of clinical inspection of the nail unit is enhanced by epiluminescence magnified examination through the nail plate, and this is sufficient to suggest that the dermoscope is an additional tool for clinical examination. However, the precise description of infraclinical symptoms and the ability to record dermoscopic images and to use them for further comparisons, clinico-pathological correlations, or telediagnosis are, in the authors’ view, important enough to allow us to consider dermoscopy as another way of “imaging” the nail apparatus.

Dermoscopy has been used for many years in the differential diagnosis of pigmented skin tumors and has been proven superior to naked-eye examination in the differential diagnosis of melanoma on the skin [1, 2]. It therefore seems logical that this technique was first used on the nail unit to better establish the differential diagnosis of nail pigmented longitudinal bands (also known as melanonychia striata). After the publication by Ronger et al. [3], several reports have further analyzed pigmented longitudinal bands of the nail plate. Even though some doubts have been expressed about the real value of dermoscopy of the nail [4], many reports conclude that there is an increased accuracy of diagnosis of nail tumors with dermoscopy compared with the naked eye [5–13].
Equipment/technical aspects

Dermoscopy of the skin is nothing more than magnified examination of a lesion with a lighting system that suppresses the reflectance of the light by the stratum corneum or the superficial structures of the nail plate. This result could be achieved either by 20° tangential lighting of the lesion combined with immersion in a liquid or gel and a magnification lens (contact dermoscopy) or by examination of the lesion through a magnifying lens with polarized illumination of the examined zone (non-contact and/or contact polarized light dermoscopy). Both systems are commercially available and produce similar results on the nail unit, but most published images have been obtained by contact immersion dermoscopy. In this case, the choice of a solution or gel to suppress the air–skin interface and therefore the reflectance of the light by the bright nail plate surface is much more favorable than the use of more fluid interface solutions such as water or alcohol solutions used elsewhere on skin [14]. The authors favor the use of an antiseptic gel (Purell®, Johnson & Johnson, USA).

Examination is performed by either contact (Fig. 4.1) or non-contact polarized light (Fig. 4.2) dermoscopy and photographs can be taken with commercially available devices (Fig. 4.3). Examination is not limited to the surface of the nail and perionychium, as useful information can also be gained by dermoscopic examination of the free edge of the nail plate (Fig. 4.4; see “Nail plate free edge examination”) and by non-contact polarized light during operative examination of the nail matrix (Fig. 4.5; see “Intraoperative non-contact polarized light dermoscopy of the nail matrix”).

In addition, special devices permit the recording of dermoscopic images for the purpose of further

Figure 4.1 Immersion contact dermoscopy.

Figure 4.2 Polarized light non-contact dermoscopy.

Figure 4.3 Photodermoscopy with an immersion contact non-polarized optical system (a), clinical image of a nail matrix nevus (b), and dermoscopic image of the same nail matrix nevus (c).
Dermoscopy comparison. These complex systems, also known as digital dermoscopy follow-up tools, are mainly used to follow the skin lesions of patients at high risk for melanoma but can also be used in cases of controversial nail unit pigmented lesions to better decide which cases should be submitted for nail matrix biopsy if changes occur over time (Fig. 4.6; see "Digital dermoscopy follow-up").

**Basic dermoscopic semiology on nails** [3, 7, 11]

**Blood spots**

Blood spots have a sharp, round-shaped proximal edge and a somewhat filamentous distal edge. Their color varies from purple-red in recent lesions to black-brown in older ones. They are observed in cases of trauma-induced subungual hemorrhages but their diagnosis might be difficult if the trauma was not important enough to be remembered by the patient. This is typically the case with repetitive microtrauma-induced subungual hemorrhages of the toenail due to tight or badly fitting shoes (Figs 4.7, 4.8). Blood spots are also observed in malignant tumors of the nail unit and their occurrence can be facilitated by anticoagulation or platelet antiaggregant therapy (Fig. 4.9). Since bleeding can mask the clinical signs of an underlying tumor, reexamination of the patient after 4–6 months (remembering that subungual hemorrhages move distally about twofold more slowly than the nail plate itself) is mandatory.

**Brown background to the pigmentation**

A brown background of the longitudinal band indicates that significant melanocytic hyperplasia exists in the nail matrix. This is observed in nail matrix nevi and pigmented melanomas. The color may vary from light brown to dark brown and even black. The darkness of the color usually reflects the skin type of the patient. Patients with Fitzpatrick’s skin types I, II, and IIIa more often show a light brown coloration whereas types IIIb, IV, V, and VI show a darker one (Figs 4.10–4.12).
Gray or gray-yellowish background to the pigmentation

On dermoscopy of the nail plate, gray color of the band generally indicates that no prominent melanocytic hyperplasia is present in the nail matrix. It is observed in many conditions: lentigo and lentiginoses of various types, ethnic-type pigmentation, drug-induced pigmentation, and repetitive trauma-induced (mostly frictional on toenails) pigmentation. Rarely, it may also be seen in very early cases of in situ melanoma, justifying digital dermoscopy follow-up in doubtful cases. As in the skin, Bowen disease (squamous cell carcinoma in situ) can also be pigmented and in this case the coloration in

Figure 4.6 Digital dermoscopy of the nail unit (a). Significant changes are observed over 1 year in a case of nail matrix in situ melanoma (b).
dermoscopy is often gray rather than black (Fig. 4.13), as also occurs in periungual Bowen disease (Fig. 4.14). In these two latter cases, Bowen disease is regularly monodactylc whereas other conditions generally affect multiple nails (Figs 4.15, 4.16).

**Regular pattern of parallel microlines**

When superimposed over a brown background, thin longitudinal microlines can be observed with dermoscopy. When their color, thickness, spacing, and parallelism are regular, whatever the depth of their color, which reflects the skin type of the patient, the pattern is called “regular” (Figs 4.17, 4.18). This regular pattern is observed in benign melanocytic nevi of the nail matrix.

**Figure 4.7** Blood spots have a sharp round proximal edge and a somewhat filamentous distal edge. Their color varies from purple-red in recent lesions to black-brown in older ones.

**Figure 4.8** Blood spots of different ages in a repetitive trauma-induced subungual hemorrhage. Note that the color varies from one area to another and that the proximal edge of the largest spots is round whereas the distal part shows a parallel linear pattern.

**Figure 4.9** Invasive squamous cell carcinoma of the left thumbnail revealed by a subungual hemorrhage after the initiation of anticoagulation treatment. Note the longitudinal leukoxanthonychia (a), the multiple splinter hemorrhages (b), and the distal hyperkeratosis underneath the nail plate (c).
Figure 4.10  Brown background of the longitudinal band indicates that significant melanocytic hyperplasia exists in the nail matrix (nevus or melanomas).

Figure 4.11  Light brown background color in a benign nail matrix nevus in a Fitzpatrick’s type II patient. The darkness of the brown color has no diagnostic significance. It generally reflects the skin type (phototype) of the patient.

Figure 4.12  Dark brown background color in a benign nail matrix nevus in a Fitzpatrick’s type IV patient. The darkness of the brown color has no diagnostic significance. It generally reflects the skin type (phototype) of the patient.

Figure 4.13  Pigmented Bowen disease (in situ squamous cell carcinoma) of the right thumbnail of a professionally irradiated patient. Note the gray coloration of the band and the subtle subungual hyperkeratosis on dermoscopic examination of the free edge.
Figure 4.14  Bowen disease (in situ squamous cell carcinoma) of periungual skin. Dermoscopic criteria of Bowen disease of the skin apply in this case: presence of scattered glomerular vessels, gray pigmentation, and irregular desquamation.

Figure 4.15  Dermoscopic gray color of the band indicates that no prominent melanocytic hyperplasia is present in the nail matrix. It is encountered in many conditions: lentigo and lentiginoses of various types, ethnic-type pigmentation, drug-induced pigmentation, and repetitive trauma-induced (mostly friction on toenails) pigmentation. It may also be seen in very early cases of in situ melanoma or in Bowen disease. In these latter cases, it is regularly monodactylic whereas other conditions generally affect multiple nails.

Figure 4.16  Ethnic-type pigmentation in a Fitzpatrick’s type V patient. Note that the phenomenon is observed in multiple locations and that the color is grayish.
Irregular pattern of longitudinal parallel microlines

In contrast, when the color, thickness, and spacing are irregular and vary from one area to another and when, usually in more advanced cases, areas of disruption of the parallelism are observed, the pattern is called “irregular” (Figs 4.19, 4.20). It is the principal dermoscopic symptom of pigmented melanoma and its presence mandates a biopsy of the nail matrix.

Micro-Hutchinson’s sign

Clinically Hutchinson’s sign is defined by the pigmentation of the periungual skin around a hyperpigmented nail plate. It is considered a warning sign highly suggestive of melanoma. It is also found in congenital nevi of the nail. It must not be confused with pseudo-Hutchinson’s sign, which is visibility of the pigmented band of the nail plate through a translucent cuticle and which has no particular diagnostic significance. With dermoscopy, it is possible to observe very subtle pigmentation of the cuticle or of the submatrix, almost invisible to the naked eye and called the “micro-Hutchinson’s” sign (Figs 4.21, 4.22). In the authors’ experience, this rare sign is almost only observed in melanoma yet might be seen in atypical ethnic-type pigmentation and in congenital nevi of the nail unit.

Atypical Hutchinson’s sign

Atypical Hutchinson’s sign is defined by the presence of at least one of the two major dermoscopic criteria for
Dermoscopy

121

melanoma in acral sites in the periungual skin: parallel ridge pattern (Figs 4.23, 4.24) and/or irregular diffuse pigmentation. The parallel ridge pattern is only observed in the anterior aspect of the hands and posterior aspect of the feet distal to Wallace’s line, which separates the palmarplantar skin (with fingerprints) from the glabrous skin. It is recognized by the presence of pigment in large parallel bands separated by a thin unpigmented parallel band. Hyperpigmentation of the (large) ridges of the fingerprints contrasting with the (thin) unpigmented furrows was first described in palm and sole melanoma by opposition with the hypopigmentation of the (thin) furrows contrasting with the hyperpigmentation of the (large) ridges that constitutes the hallmark of palm and sole nevi (Figs 4.23, 4.24). In cases of nail unit melanoma, irregular diffuse pigmentation is more often found on the supramatrical skin whereas the parallel ridge pattern is only found on the finger/toe tip, the pulp of the finger/toe, or around the lateral nail folds.

**Longitudinal xantholeukonychia**

Band-like white coloration of the plate is called leukonychia and yellow coloration is called xanthonychia. These two

---

**Figure 4.21** Micro-Hutchinson’s sign: presence of subtle true pigmentation of the cuticle or of the supramatrical skin almost invisible to the naked eye. This must not be confused with the pseudo-Hutchinson’s sign, visible in Fig. 4.20, that corresponds to the simple visibility of the nail plate pigmentation through a translucent cuticle.

**Figure 4.22** Micro-Hutchinson’s sign: presence of subtle true pigmentation of the supramatrical skin almost invisible to the naked eye in a Clark’s level II acral lentiginous nail matrix melanoma of thickness 0.18 mm.

**Figure 4.23** Atypical Hutchinson’s sign defined by the presence of at least one of the two major dermoscopic criteria for melanoma in acral sites in the periungual skin: parallel ridge pattern (shown here) and/or irregular diffuse pigmentation.

**Figure 4.24** Atypical Hutchinson’s sign: parallel ridge pattern recognized by the presence of the pigment in large parallel bands separated by thin unpigmented parallel bands reflecting the hyperpigmentation of the ridges of the fingerprints and contrasting with the unpigmented furrows in an advanced partially amelanotic nail matrix Clark’s level IV acral lentiginous melanoma of thickness 3.2 mm.
colors are often observed simultaneously within the same lesion (Figs 4.25, 4.26).

Band-like longitudinal splinter hemorrhages

Splinter hemorrhages are found in the nail in many conditions, including connective tissue diseases, onychotillomania, disorders of coagulation or nutrition, and hematological disorders. In such cases, they are found on several nails and, on any one nail, involvement is not limited to only a part of the nail plate. When splinter hemorrhages, often in association with other signs such as leukoxanthonychia or polychromia, are limited to a band on the nail plate, an epithelial tumor of the nail matrix should be suspected (Figs 4.27, 4.28). Splinter hemorrhages are also often associated with nail unit amelanotic melanoma yet their disposition is less systematized along the plate.

Longitudinal erythronychia with enlarged proximal origin

Cherry (senile) hemangiomas of the nail plate are not uncommon and their dermoscopic aspect is, in many cases, characterized as a longitudinal thin erythronychia with a clubbed proximal edge (Figs 4.29, 4.30).
Localized subungual hyperkeratosis and distal triangular plate erosion

Dermoscopic examination of the free edge of the nail plate at the distal extremity of a longitudinal abnormality, in most cases leukoxanthonychia often with splinter hemorrhages and not uncommonly with polychromia, often shows a localized subungual hyperkeratosis (Figs 4.31, 4.32). This often indicates the presence of an epithelial tumor of the nail matrix (onychomatricoma, onychopapilloma, squamous cell carcinoma, or seborrheic keratosis). A triangular erosion of the distal nail table indicates the presence of a subungual tumoral syndrome, but the etiology cannot be predicted.

Polychromia

Polychromia is defined by the presence of four or more of the following colors: black, red, blue, white, yellow, dark brown, light brown, gray, or purple. Polychromia is very often observed in malignant amelanotic neoplasms such as squamous cell carcinoma or amelanotic melanoma (Figs 4.33, 4.34).
Atypical vessels [15]

In dermoscopy, an atypical pattern of the vessels is defined by at least one of the following criteria (Figs 4.35, 4.36):

- presence of at least three different types of vessels (dots and globules, comma-like, hairpin-like, linear, corkscrew-like, arborizing) within the same lesion
- presence of linear and irregular vessels (caliber changes from one segment to another of the same vessel)
- milky-red areas defined as structureless pink areas with various shades of pink without identified vascular structures; these areas are found in pyogenic granuloma and in advanced amelanotic melanoma (the two being impossible to differentiate on the basis of clinical or dermoscopic examination so biopsy for histopathological examination is mandatory).

Figure 4.32 Onychopapilloma: note the longitudinal erythronychia is not clubbed at its proximal edge, and the presence of localized hyperkeratosis underneath the nail plate in the area corresponding to the visible longitudinal band.

Figure 4.33 Polychromia defined by the presence of four or more colors among the following list: black, red, blue, white, yellow, dark brown, light brown, gray, and purple. Polychromia is very often observed in malignant amelanotic neoplasms such as squamous cell carcinoma or amelanotic melanoma.

Figure 4.34 Dermoscopic polychromia (red, white, gray, light brown) in a nail matrix melanoma Clark’s level III acral lentiginous melanoma of thickness 1.5 mm.

Figure 4.35 Atypical pattern of the vessels is dermoscopically defined by at least one of the following criteria: presence of at least three different types of vessels (dots and globules, comma-like, hairpin-like, linear, corkscrew-like, and/or arborizing) within the same lesion; presence of linear and irregular vessels (caliber changes from one segment to another of the same vessel); or milky-red areas.
Yellow spot

A yellow well-demarcated structureless round or ovoid spot is observed in subungual exostosis. It is created by the pressure of the bone on the nail bed tissue underneath a firm plate (Figs 4.37, 4.38).

Red spots

Structureless red spots are observed in areas of nail plate erosion or through the nail plate. Their significance is close to “milky-red areas” and should lead to a biopsy to differentiate amelanotic melanoma from pyogenic granuloma (Figs 4.37, 4.39).

Purple-blue spot

A structureless purple or blue spot is observed through the nail plate mainly in two conditions: the extremely rare blue nevus of the nail unit and the very common glomus cell tumor. In the latter, the pressure of the dermoscope on the nail plate can trigger the characteristic “electric” pain of this neoplasm (Figs 4.37, 4.40).
Advanced dermoscopy techniques

Nail plate free edge examination

Examination of the nail plate free edge (Fig. 4.4) permits the observation of subungual localized hyperkeratosis in epithelial tumors of the nail matrix such as Bowen disease, squamous cell carcinoma, onychopapilloma, onychomatricoma, and seborrheic keratosis (Figs 4.9, 4.26, 4.28, 4.32, 4.41–4.43). In onychomatricoma, its remarkable “dotted” free edge surface constitutes another criterion in favor of this diagnosis (Fig. 4.26). In onychopapilloma, the sharp “spine-shaped” hyperkeratotic plug...
visible underneath the nail plate in the area of nail changes is also very helpful (Fig. 4.32).

It is also of interest to dermoscopically examine the distal free edge of the nail plate in cases of melanonychia striata [16] since the position of the pigment in the nail plate gives an interesting indication of the location of the pigmented lesion with the matrix (i.e. proximal versus distal matrix). Since the dorsal aspect of the nail plate is derived from the proximal matrix, the presence of the pigment in the upper part of the nail plate free edge will indicate the site of the causal lesion in the proximal part of the matrix. In contrast, the presence of pigment in the lower part of the nail plate will favor a distal matrix location of the causative lesion (Figs 4.4, 4.44). Knowing or estimating the location of a pigmented lesion preoperatively is of tremendous importance in order to inform the patient of the possible esthetic consequences of the biopsy. A biopsy taken from the distal matrix will create a nail plate with an almost invisible defect from underneath, whereas a biopsy of the proximal matrix will cause a visible defect of the nail plate surface [17].

Intraoperative non-contact polarized light dermoscopy of the nail matrix

With non-contact polarized light dermoscopy, it is possible to examine the nail matrix during the surgical biopsy procedure without risk of microbial contamination of
either the exposed nail matrix or the sterile surgical instruments (Fig. 4.5). In 2005 Hirata et al. [18] proposed the perioperative examination of the nail matrix and described the streaks, pigment network, and globules in the nail matrix and nail bed in conditions characterized by nail matrix melanocytic hyperplasia (Figs 4.45, 4.46) whereas diffuse homogeneous pigmentation was observed in conditions without prominent melanocytic hyperplasia of the nail matrix such as ethnic-type pigmentation [18, 19]. Moreover, we consider that intraoperative dermoscopic examination of the nail bed and the nail matrix permits a more precise targeting of the biopsy than might occur with simple examination using the naked eye. This could also be applied in non-pigmented subungual tumors such as small squamous cell carcinoma (Fig. 4.47), glomus cell tumor [20], onychopapilloma, or onychomatricoma [21] (Fig. 4.48).

The same authors also proposed ex vivo dermoscopic examination of the nail matrix biopsy. This can be performed with contact immersion dermoscopy and provides much sharper images with similar observations (Figs 4.45–4.47, 4.49).

We must add that ex vivo reflectance confocal microscopic examination is also possible and allows detailed visualization at the cellular level (Fig. 4.49). Indeed, additional work is needed to evaluate ex vivo reflectance confocal microscopic examination of nail matrix pigmented tumors.

Digital dermoscopy follow-up

On skin, dermoscopy has been proven efficient (level of proof, A) to accurately distinguish melanoma from other pigmented lesions [1], but its sensitivity does not reach 100%. For this reason, digital follow-up of high-risk patients and of flat doubtful lesions has been developed. By sequential dermoscopic imaging of the lesion(s) and comparison of images over time, digital dermoscopy permits determination of minor changes in shape, color, or architecture of a given lesion to allow an even earlier diagnosis of melanoma than would be possible with classic dermoscopy. Many publications have validated the concept of sequential dermoscopic imaging of cutaneous lesions in order to make a more accurate and precise diagnosis of melanoma (level of proof, B) [22], but even though the situation appears to be similar for nails, the value of digital sequential imaging of doubtful cases of melanonychia striata has not yet been evaluated in published prospective studies. However, the authors have some experience with sequential dermoscopy and believe that, in selected indications, digital follow-up of nail pigmentation could help to demonstrate changes over time and therefore aid the diagnosis of suspected melanoma in patients in whom both clinical and dermoscopic criteria are at first insufficient to permit its positive diagnosis. Since the concept has not been established in large series, this technique is mentioned briefly here. However, it is the authors’ opinion that prospective large studies are definitively needed to better establish the role and impact of digital dermoscopy follow-up of nail pigmentation (Figs 4.6, 4.50, 4.51).

Dermoscopy-based differential diagnoses

Nail matrix melanocytic nevus

Nail matrix melanocytic acquired nevi are dermoscopically characterized by their brown background coloration
Figure 4.45  Nevus of the nail matrix in an 18-year-old male patient (a). Immersion dermoscopy of the nail plate (b) shows a regular pattern of the longitudinal lines. Intraoperative non-contact polarized light dermoscopy (d) better reveals the limits of the lesions than naked eye observation of the surgical field (c). Because streaks and globules are present, suspicion of a neoplasm is increased with melanocytic hyperplasia. Ex vivo immersion dermoscopy shows even more precisely the streaks and globules (e).

Figure 4.46  Nail matrix in situ melanoma in a 24-year-old male patient (a). Immersion dermoscopy of the nail plate shows an irregular pattern of the longitudinal lines (b). Moreover, intraoperative non-contact polarized light dermoscopy (c) and ex vivo immersion dermoscopy (d) of the nail matrix show the presence of streaks and globules and their asymmetrical and irregular architectural arrangement.
and the regular pattern of the longitudinal microlines (Figs 4.10–4.12). Congenital nevi may exhibit atypical patterns and their differentiation from melanoma is very difficult on the basis of clinical and dermoscopic features. Therefore careful follow-up is mandatory.

Nail matrix pigmented melanoma

In cases of melanonychia striata in a postpuberty patient, melanoma should be included in the differential diagnosis list [10]. Clinical warning signs are adult onset, monodactylic involvement, changes over time observed by the patient, triangular shape of the band (indicating that the lesion is growing relatively faster than the nail plate), polychromia, and the presence of pigmentation of the periungual skin (also known as Hutchinson’s sign). Dermoscopy provides useful additional information: the coloration of the background is light brown to black and the longitudinal dermoscopic microlines are irregular in their thickness, spacing, and coloration and may show areas of parallelism disruption (Figs 4.19, 4.20, 4.52). Brown-to-black dots and globules may be observed in association with the longitudinal lines (Fig. 4.22). Dermoscopic examination of periungual skin may disclose a micro-Hutchinson’s sign (Figs 4.21, 4.22, 4.53) invisible to the naked eye. In cases of prominent periungual pigmentation, its dermoscopic features produce either a parallel ridge pattern on the pulp, the lateral aspects, and/or the distal aspects of the finger/toe (Figs 4.23, 4.24) or a diffuse irregular pigmentation on the supramatrical skin (Fig. 4.54). Careful attention...
must be paid to cases in which the irregular pattern of
the lines is associated with subungual hemorrhage
(Fig. 4.55).

**Nail matrix amelanotic melanoma**

Amelanotic melanoma of the nail unit is very often a late
presentation of the disease after several months/years of
the undiagnosed condition, which often includes typical
monodactylic melanonychia striata [23, 24]. At this stage,
partial or complete erosion of the nail plate is observed
and the pigmentation that the patient eventually recalls
has vanished, to be replaced by an often exo­phytic,
ulcerative, bleeding tumor. Differential diagnosis
includes pyogenic granuloma and several infectious
conditions but, as a rule, amelanotic melanoma should
be systematically included in cases of monodactylic nail
plate erosion with or without nodular and erosive tumor.

In this case, dermoscopy reveals features that have been
described on amelanotic melanoma of the skin [15].

It shows an atypical vascular pattern characterized by
the presence of linear and irregular vessels, the presence
of milky-red areas or the presence of three or more types
Figure 4.51 Clinical (a) and dermoscopic (b) views of melanonychia striata of the second right fingernail in a 45-year-old female patient. Neither clinical nor dermoscopic features observed on all four images are sufficient to accurately diagnose this acral lentiginous in situ melanoma. Changes observed over such a short period of follow-up meant that this case had to be submitted to the pathologist before any clue to melanoma could be observed.

Figure 4.52 Clark's level II acral lentiginous melanoma of the left great toenail of thickness 0.35 mm. Note the atypical pattern of the longitudinal microlines with irregularity in color spacing and thickness.

Figure 4.53 Clark's level II acral lentiginous melanoma of the nail matrix of thickness 0.15 mm on the right fourth fingernail. Pattern of the longitudinal microlines is regular but the presence of a micro-Hutchinson's sign allowed an early diagnosis to be made.

Figure 4.54 Clark's level III acral lentiginous melanoma of the right thumbnail of thickness 0.7 mm. Note the irregular pattern of the longitudinal microlines but also the presence of an atypical Hutchinson's sign with diffuse irregular pigmentation.

Figure 4.55 Acral lentiginous in situ melanoma with a simultaneous subungual hemorrhage of the left thumbnail. The lesion was recognized by the irregular pattern of the longitudinal microlines.
of vessel within the same lesion (Figs 4.35, 4.36, 4.56, 4.57). In a few cases, only red spots seen through the nail plate or in areas of plate erosion are visible (Figs 4.37, 4.39). It is also possible to identify subtle areas of pigmentation, invisible to the naked eye and incorrectly but traditionally called “remnants” of pigmentation (Fig. 4.39).

**Congenital or congenital-type nevi of the nail unit**

Nail unit melanoma in children is extremely rare and very difficult to diagnose [25]. Moreover, unfortunately, clinical as well as dermoscopic criteria used in adults cannot be applied to children since congenital nevi of the nail unit are characterized by signs that are considered extremely suspicious of melanoma in adults [26–30]. Triangular shape of the band, irregularity of its pigmentation, nail plate softening or erosion, and periungual pigmentation are very common features of congenital (or congenital type) nevi of the nail unit. For these reasons, the International Society for Dermoscopy (IDS) has created an international register of congenital and congenital-type nevi of the nail unit. To date, this register has included more than 150 cases worldwide of pigmented lesions of the nail unit either present at birth or diagnosed during the first 5 years of life. This ethical committee-approved register is located in Lyons, France, and held by Lyon 1 Claude Bernard University Dermatology Department. Details for submission of cases can be found on the IDS website [31, 32].

Since this observational study is still ongoing, we will only include here, with a few illustrations, some of the preliminary findings. We commonly determined that an irregular pattern of the dermoscopic longitudinal micro-lines is seen (Figs 4.58, 4.59) as well as a triangular shape of vessel within the same lesion (Figs 4.35, 4.36, 4.56, 4.57). In a few cases, only red spots seen through the nail plate or in areas of plate erosion are visible (Figs 4.37, 4.39). It is also possible to identify subtle areas of pigmentation, invisible to the naked eye and incorrectly but traditionally called “remnants” of pigmentation (Fig. 4.39).
of the whole band (Fig. 4.60). Periungual involvement, also known as Hutchinson’s sign, was also a very common finding, with a remarkable tropism for the toe/fingertip (Figs 4.61–4.63). The pigmentation in the skin distal to the hyponychium often had a longitudinal and parallel disposition perpendicular to the dermatoglyphics. In rare cases with extremely wide involvement of the periungual skin, a disposition of the pigment along the furrows of the dermatoglyphics, reproducing the classic parallel furrow pattern [33] of benign acral nevi, was observed (Fig. 4.62). It was also found that a more regular pattern of the pigmentation appeared after a few years of evolution (Fig. 4.64) and that, in some cases, the pigmentation faded away almost completely (Fig. 4.65).

Inclusion of new cases in the register [31, 32] is greatly needed and encouraged in order to increase our knowledge of the natural history of congenital nevi of the nail matrix and to better codify the management of these very difficult cases.

Figure 4.60 Congenital nevus of the left thumbnail in a 5-day-old female patient. Note the triangular shape of the nail pigmented band.

Figure 4.61 Congenital nevus on the second right toenail in a 2-year-old female patient. Note the irregular pattern (in color, thickness, and spacing) of the longitudinal dermoscopic pigmented microlines. Note also the presence of a marked periungual involvement (Hutchinson’s sign) and its peculiar tropism for the tip of the toe with a somewhat parallel linear arrangement perpendicular to the dermatoglyphics.

Figure 4.62 Congenital nevus on the third right toenail in a 1-year-old skin type VI female patient. Note the completely black nail. Note also the presence of a marked periungual involvement (Hutchinson’s sign) and its peculiar tropism for the tip of the toe with a somewhat parallel linear arrangement perpendicular to the dermatoglyphics in the vicinity of the hyponychium whereas it shows some tendency to have a parallel furrow pattern in its distal part.

Figure 4.63 Congenital nevus on the fourth right toenail in a 3-year-old female patient. Note that the nail plate is almost uninvolved whereas there is a periungual pigmentation (Hutchinson’s sign) both above the proximal nail fold and in the distal portion of the plate with this peculiar parallel longitudinal disposition of the pigmentation perpendicular to the dermatoglyphics.

Figure 4.64 Evolution after 3 years in the patient shown in Fig. 4.60. Note the much more regular pattern of the dermoscopic pigmented longitudinal microlines.

Figure 4.65 Evolution after 7 years of the patient shown in Figs 4.60 and 4.64. Note the progressive fading away of the pigmentation over time.
Subungual hemorrhage [3, 34]

Subungual hemorrhage is a very common condition. Its diagnosis is easy when there is a clear history of trauma. However, the diagnosis is more difficult if the patient does not remember any history of trauma, especially when the lesion is created by repetitive trauma due to tight or badly fitting shoes (especially during exercise as occurs in runners and hikers) (Fig. 4.8). In some cases, subungual bleeding is facilitated by an anticoagulant or platelet antiaggregant therapy (Fig. 4.9). Careful dermoscopic examination is required in these cases because bleeding does not exclude an associated tumor. In order to safely make the diagnosis of simple subungual hemorrhage, it is mandatory that only blood spots (Figs 4.7, 4.8) should be observed with dermoscopy. If any other signs are seen (Figs 4.9, 4.55), this hypothesis must be rejected. Moreover, careful reexamination of the patient after 2–6 months is absolutely necessary in order to make sure that no underlying tumor was present and masked by the bleeding (remembering that subungual hemorrhages move distally about twofold more slowly than the nail plate is growing).

Nail unit lentigo or lentiginoses [3, 35, 36]

Lentigo and lentiginoses of various types (e.g. Laugier–Hunziker, Peutz–Jeghers, or Carney complex) may affect the nail unit. Examination of other involved areas and consideration that the nail pigmentation is polydactylic greatly aid in diagnosis. Dermoscopy shows a gray band-like pigmentation (Figs 4.15, 4.66). Follow-up of these patients might be difficult since additional longitudinal pigmented bands may occur over time.

Repetitive trauma-induced longitudinal pigmentation

In Fitzpatrick’s type IIIb, IV, and V patients, postinflammatory and particularly posttraumatic pigmentation of the skin is not uncommon. This phenomenon also occurs on the nails. An excellent example of this occurs in cases of symmetrical pigmentation of the fifth toenail in women due to tight-fitting shoes. Self-provoked repetitive trauma of the nail in onychotillomania may also cause longitudinal pigmentation (Fig. 4.67). Dermoscopic diagnosis is based on the observation of a gray pigmentation of the band (Figs 4.15, 4.67). In a few cases, the pigmentation can vanish after suppression of the causative repetitive trauma.

Ethnic-type pigmentation

Ethnic-type pigmentation is also often a polydactylic condition and family history helps in its diagnosis. As it predominates on the right hand in right-handed patients (and the opposite in left-handed) and occurs in dark-skinned persons, it is likely that it could also correspond to some kind of repetitive trauma-induced pigmentation. Nevertheless, the dermoscopic aspect is similar, involving a grayish subtle dermoscopic pigmentation (Fig. 4.16).

Drug-induced pigmentation

Many drugs can induce pigmentation of the nail plate, among them hydroxyurea, bleomycin, and minocycline, with zidovudine (AZT) being the most common. Dermoscopic features are very similar to those observed in lentiginoses with polydactylic gray longitudinal bands (Fig. 4.68).

Squamous cell carcinoma, Bowen disease

 Bowen disease, also known as in situ squamous cell carcinoma [37], can affect the nail and the periungual skin or both, and in rare cases it is polydactylic. Nail involvement can reveal a white-to-yellow longitudinal discoloration of the nail plate but pigmented cases are...
not uncommon. In the latter case, pigmentation is often grayish rather than brown or black. Other features of epithelial tumors of the matrix may be observed and include band-disposed splinter hemorrhages, polychromia, and subungual localized hyperkeratosis (Fig. 4.13). Periungual involvement reproduces the dermoscopic features observed in cutaneous Bowen disease: the presence of irregular desquamation, glomerular (round-shaped at classic × 10 or × 20 dermoscopic magnification but exhibiting a tridimensional pattern resembling the glomerulus apparatus of the kidney at higher magnification) vessels grouped in bunches and dust-like gray pigmentation [38] (Fig. 4.14). Invasive squamous cell carcinoma exhibits quite similar but more prominent features [39] with more common bleeding, thicker localized subungual hyperkeratosis, and polychromia.

In some cases, the lesion is painful and the pain can be triggered by the pressure induced by the dermoscope (Figs 4.9, 4.41–4.43).

**Onychomatricoma**

Onychomatricoma exhibits the same dermoscopic features as squamous cell carcinoma but with less architectural disorder and more symmetry, and its demarcation from normal uninvolved nail is sharply delineated. Examination of the free edge of the nail plate can reveal the characteristic punctuations of onychomatricoma. However, in our view, dermoscopic differential diagnosis between onychomatricoma and squamous cell carcinoma (and onychopapilloma) remains difficult [40] (Figs 4.26, 4.69).

**Onychopapilloma**

Dermoscopic features of onychopapilloma [41] do not differ much from those observed in other epithelial tumors of the nail matrix (i.e. squamous cell carcinoma, onychomatricoma, and seborrheic keratosis). However, in onychopapilloma, the width of the yellow-white band with occasional splinter hemorrhages and some polychromia is much smaller and demarcation from the surrounding uninvolved nail plate is sharp and parallel. Moreover, the subungual hyperkeratosis is also extremely limited and produces a kind of hyperkeratotic spine underneath the nail plate that the patient has usually noticed and that is painful. Occasionally, bleeding occurs during attempts to trim it while cutting off the nail distal edge (Fig. 4.32).
Nail unit seborrheic keratosis

Nail unit seborrheic keratosis is a very rare entity [42]. Its dermoscopic features are similar to other epithelial tumors of the nail matrix with whitish-yellowish longitudinal bands with band-disposed splinter hemorrhages and subungual localized hyperkeratosis. However, a helpful additional feature is the presence of white, round-shaped “milia-like” cysts that are observed through the translucent nail plate very similar to the milia-like cysts observed in cutaneous seborrheic keratoses (Fig. 4.28).

Blue nevus of the nail unit

Blue nevus of the nail unit is also a very rare entity [43]. Dermoscopically, it corresponds to a blue proximal spot which is stable over time. In the authors’ view, the disease is rare enough to justify surgical exploration of the nail matrix and excision of the lesion (Fig. 4.70).

Glomus cell tumor

Glomus cell tumors of the nail unit are very common and diagnosis is greatly helped by the typical “electric” pain caused by the lesion after minor trauma of the involved nail. Dermoscopy [44] shows a purple-red well-circumscribed spot that may be located anywhere underneath the nail plate. Dermoscopy is also of great help to preoperatively locate the lesion precisely before surgical treatment (Figs 4.40, 4.71).

Subungual exostosis

Subungual exostosis is also a very common subungual tumor. In most cases, it is isolated but rarely it is a part of the multiple exostosis syndrome. The existence of these tumors justifies the rule that every subungual tumoral syndrome should be radiographically imaged, which should prove the diagnosis and codify the surgical treatment. However, the diagnosis can be suspected before the imaging procedures by dermoscopic examination through the nail plate, which discloses a sharply circumscribed yellow spot made even more visible by applying some pressure with the dermoscope on the overlying nail plate (Fig. 4.38).

Subungual cherry hemangioma

Cherry (senile) hemangiomas are very common on the skin after the age of 40 years. Dermoscopy shows a
proximally clubbed red longitudinal band with no other change of the nail plate and especially no localized hyperkeratosis underneath the nail plate. In the authors’ view, this image is typical enough to avoid unnecessary (and painful) surgery of such cases (Figs. 4.29, 4.30).

References


www.dermoscopy–ids.org/

www.dermoscopy–ids.org/index.php/studies


Chapter 5

Ultrasound and Other Imaging Methods

Ximena Wortsman¹, Gregor B.E. Jemec², and Axel Villani³

¹ Institute for Diagnostic Imaging and Research of the Skin and Soft Tissues; Departments of Dermatology, University of Chile and Pontifical Catholic University of Chile, Santiago, Chile
² Department of Dermatology, Zealand University Hospital, Roskilde; Health Sciences Faculty, University of Copenhagen, Copenhagen, Denmark
³ Dermatology Department, Edouard Herriot Hospital, Lyon 1 Claude Bernard University, Lyon, France

ULTRASOUND IMAGING OF THE NAIL

Introduction

Ultrasound, an imaging technique based on the emission of sound waves, has evolved to become a routine imaging tool for studying the nail in real time. In contrast with radiographs and computed tomography (CT), ultrasound is a non-radiating diagnostic imaging modality. Therefore, it is safe and, usually, cost-effective to use; it is also available worldwide. Moreover, ultrasound allows the nail to be observed from the surface of the nail plate to the bony margin of the distal phalanx without the penetration issues that arise in other imaging modalities used in dermatology. Also, ultrasound does not require the patient to be confined in a small and noisy space, as in, for example, magnetic resonance imaging (MRI). Furthermore, in contrast to CT and MRI, ultrasound does not usually require intravenous contrast. This significantly reduces potential adverse reactions such as allergies, nephrogenic fibrosis, or nephrotoxic effects [1].

Thus, ultrasound can provide detailed anatomic information with high definition of the nail and its common pathologies. However, as with any other medical procedure, this imaging technique requires a trained operator and the correct equipment. If the latter conditions are present, ultrasound can become a powerful imaging technique with few limitations. It can provide rapid access to subclinical data that may be difficult to obtain by clinical examination alone or by using other imaging modalities.

Ultrasound shows a real-time window that can look very similar to lower magnification histological images. However, ultrasound is currently not able to provide anatomic information on the medulla of the bone because sound waves cannot pass through compact bony structures. Nevertheless, the cortex of the bone can be detected. In the latter case, radiographs, CT, or MRI may be a more suitable indication for observing the medulla of the bone, according to the complexity of the pathology.
On the other hand, ultrasound can show submillimeter structures and discriminate characteristics of the tissues that would be difficult to detect with commercially available CT or MRI units [1].

The nail unit is a complex anatomic structure closely attached to the surrounding tendinous, articular, and bony tissue [2, 3]; therefore, it can be primarily or secondarily affected by multiple conditions. Clinical diagnosis often requires specialist knowledge, and nail disorders are challenging because the ungual plates often mask their signs. Moreover, biopsies are invasive procedures that can be difficult to perform and leave permanent cosmetic sequelae [4–6].

With ultrasound, this valuable anatomic information can be registered directly on a screen without any significant limitations and can provide detailed data about the exact location, extent, and activity of a nail condition. This information may objectively affect daily practice decisions, such as incision sites and sizes, or discriminate between an inflammatory or tumoral entity, or between an ungual or periungual condition, which can support earlier diagnosis and lead to a better cosmetic prognosis. The current limitations of variable frequency ultrasound are lesions that measure <0.1 mm, those located only in the epidermis, and the detection of pigments such as melanin [1, 6–8].

**Ultrasound techniques**

The nail is examined with the finger or toe fully extended. A copious amount of gel is applied over the nail and periungual area. Thus, a compact-linear (hockey stick shaped) or linear variable frequency probe that works with frequencies ≥15 MHz is recommended for performing the examination. Sweeps that include at least two perpendicular axes (longitudinal and transverse view) are performed: first using grayscale and then using color Doppler with spectral curve analysis. The spectral curve of the blood flow is useful for demonstrating the type (arterial or venous) and velocity (cm/s) of the flow as well as the location of vessels [1, 8]. As an option, three-dimensional (3D) reconstructions can be performed by making 5–8-s sweeps commonly using the software and settings that are supplied with the machine. Color filters may be added to the plain 3D images or angio-3D reconstructions to improve the presentation. More recently, endoluminal flow detection applications (e.g. B-Flow; General Electric Health Systems, Milwaukee, WI, USA) that produce a live “echoangiogram” image have been developed [1].

**Normal sonographic anatomy of the nail**

The nail unit comprises three main areas: the plates, the nail bed (including the ungual matrix), and the periungual tissues. The dorsal and ventral plates present a bilaminar hyperechoic structure (two parallel lines) separated by a thin layer of hypoechoic tissue (interplate space) [1, 4–9]. The normal location of the origin of the plates is far from the level of the distal interphalangeal joint. The nail bed is generally hypoechoic, but usually becomes slightly hyperechoic in the dermis, which is located below the matrix area [1, 6–8]. Low-velocity arterial and venous vessels are typically detectable within the nail bed closer to the bony margin. Arterial flow comes from the paired dorsal and palmar digital arteries that arise from the arcades that are supplied from the radial and ulnar arteries. Periungual skin is present in the lateral and proximal nail folds and shows the same echogenicity as the skin layers located in the rest of the body except for the palms and soles (non-glabrous skin). The epidermis presents as a hyperechoic line, and keratin mainly provides its echogenicity; the dermis shows as a hyperechoic band, and the collagen content mostly provides its echogenicity; the hypodermis, also called the subcutaneous tissue, presents as a hypoechoic layer that corresponds to the presence of fatty lobules. In between the fatty tissue there are hyperechoic linear structures that correspond to the fibrous septa. Adipose lobules in the hypodermis are scarce in the proximal and lateral nail folds; however, this layer becomes thicker at the hyponychium and pulp of the finger. At the glabrous palmar skin, the epidermis shows a bilaminar hyperechoic structure because of the higher keratin content.

The distal insertion of the lateral bands of the extensor tendon at the distal phalanx shows a fibrillar hyperechoic pattern, typical of tendinous structures; however, it may show some hypoechogenicity because of anisotropy (i.e., an artifact due to the obliquity of the path of the tendons). The bony margin of the distal phalanx shows as a continuous hyperechoic line following the contour of the cortex of the bone that is only interrupted by the anechogenicity of the distal interphalangeal joint space that contains a laminar amount of fluid and cartilage (Fig. 5.1; Video 5.1) [1, 6–8].

**Benign pathology**

**Anatomic variants, genetic diseases, and secondary involvement**

These are challenging entities that may resemble in some cases other inflammatory or tumoral conditions. The correct identification of anatomic abnormalities may facilitate their diagnosis and monitoring.

**Congenital hypertrophic lip of the hallux**

This is also known as pseudodigital fibrous tumor of the hallux and consists of hypertrophy of the lateral fold. It is usually bilateral, symmetrical, and present at birth and mostly affects the medial aspect of the hallux [1, 8, 10–12]. Clinically, it presents as erythematous and firm swellings that may resemble recurrent digital fibrous tumors of
childhood [12]. On ultrasound, these pseudotumors consist of hypertrophic skin layers with decreased echogenicity in the upper dermis (probably related to secondary inflammation due to friction) without any true nodules or extension into the nail bed. Additionally, fragments of the nail plate may be found embedded in the lateral nail fold (Fig. 5.2) [1, 8].

Ichthyosis

The ichthyoses are a heterogeneous group of cornification disorders comprising both inherited and acquired forms. They include congenital autosomal recessive ichthyosis, which usually presents at birth, often as collodion baby, and ichthyosis vulgaris, which is the most common ichthyosis and is inherited in an autosomal dominant pattern [13, 14].

On ultrasound thickening of the nail plates with an absent interplate space and thickening of the epidermal layer in the proximal nail fold can be observed. Importantly, all changes can be objectively measured and followed up non-invasively (Fig. 5.3) [1, 8, 15, 16].

Alopecia areata

Alterations of the nails in alopecia areata have been reported previously. Hair and nails share anatomic links related to their ectodermal origin, inner components,
and frequent simultaneous involvement in many diseases [17]. Abnormalities of the nails can provide both subtle and obvious clues to common medical problems or severe systemic diseases. Nail involvement in alopecia areata is described as frequent, especially in children [18]. Clinically, pitting and varying degrees of nail dystrophies are described. Sometimes, nail changes may precede the presentation of abnormalities of the scalp, and also clinical changes may resemble psoriatic onychopathy.

On ultrasound, thickening of the proximal nail bed in comparison with the distal nail bed that also involves the matrix region may be detected. Nail plates can be hypechoic, thickened, and adopt a wavy shape. Nevertheless, on color Doppler, the nail bed is usually hypovascular in alopecia areata. The latter is in contrast to other inflammatory diseases such as psoriasis where the nail bed during active phases of the disease is commonly hypervascular. Other ultrasound signs that may be helpful to differentiate alterations from alopecia areata and...
psoriasis include the usual good definition of the ventral plate in alopecia areata; in psoriasis, areas of loss of definition of the ventral plate are commonly seen due to edema (Fig. 5.4) [1, 8].

Cystic fibrosis
This is an autosomal recessive disease resulting from mutations of the cystic fibrosis transmembrane conductance regulator gene (CFTR). A frequent finding is digital clubbing. Ultrasound examination has demonstrated a diffuse increase in the thickness and decreased echogenicity of the nail bed in the fingernails of both hands that involves the matrix region in all nails and is associated with upward displacement of the ungual plates. In some of the fingers, loss of the proximal part of the ventral plate may be detected. On color Doppler ultrasound, hypervascularity in all the fingernails of both hands, mainly affecting the proximal part of the nail beds and showing low-velocity arterial flow, has been reported [19].

Figure 5.4 Alopecia areata. (a) Clinical photograph. Courtesy of T. Saavedra. (b) Ultrasound (longitudinal view) shows thickening of the proximal nail bed (a, white vertical line) in comparison with the distal nail bed (b, white vertical line) that involves the ungual matrix in the right middle finger. (c) Three-dimensional picture of the right hallux in the same patient shows similar changes in the nail bed and wavy plates. dph, distal phalanx; m, ungual matrix; nb, nail bed; pl, plates, pnf, proximal nail fold.
Alterations of growth or location

Ingrowing toenail
This is also known as onychocryptosis and represents inflammation of the lateral fold due to the embedding of the nail plate. Commonly, it affects the great toes, and the presence of abnormalities in the axis of the nail may facilitate the development of this condition. For example, overcurvature of the nail plates (pincer nails), anomalous growth axis, or hypertrophy of the lateral nail fold, among other conditions, may favor the presentation of ingrowing toenails. Surgical treatment is common, and recurrence rates in patients without presurgical ultrasound are described as high as 70% [20, 21].

On ultrasound, it is possible to detect the exact location, axis, and diameter of the embedded hyperechoic linear fragment of the nail plate, which is usually surrounded by hypoechoic granulomatous and inflammatory tissue (Fig. 5.5). This may support decisions about the location and size of the surgical incision and potentially decrease recurrences [1, 8].

Congenital malalignment
Most common in the great toenail and based on a lateral deviation of the nail plate, probably secondary to a deviation of the nail matrix due to increased traction or hypertrophy of the extensor tendon. It may be present at birth but can also appear later in life; it can be uni- or bilateral. The most common complications are onychocryptosis and onychogryphosis.

Ultrasound can show thickening of the nail plate and bed. Hypochoicogenicity and hypovascularity of the nail bed, as well as embedded hyperechoic fragments of nail plates in the lateral nail fold, are reported [1, 8].

Onychomadesis
Also known as nail shedding, this indicates the spontaneous separation of the nail from the matrix region secondary to growth arrest. It may be detected 4–8 weeks after a severe systemic illness or significant traumatic event. Also, it can be concomitant with other chronic abnormalities of the nail.

On ultrasound two or more separated fragments of the nail plates can be identified, sometimes with an associated anechoic pseudobullous disruption in the ventral plate. Thickening and decreased echogenicity of the nail bed can also be detected (Fig. 5.6) [1, 8, 21, 22].

Retronychia
This is characterized by the posterior embedding of the nail plate into the posterior nail fold. It may be seen as a single entity or as a complication of onychomadesis. Clinically, retronychia appears 3–6 months into the course of a persistent inflammatory condition or systemic disease that disrupts nail growth. Additionally, retronychia has been detected in cases exposed to the chronic injury of the feet, such as in individuals practicing sports or after accidental trauma. In some cases, when retronychia is associated with onychomadesis, it may mimic the clinical presentation of a nail tumor.

On ultrasound, retronychia shows an abnormal shorter distance between the origin of the nail plates and the base of the distal phalanx (distal interphalangeal joint level). Thickening and decreased echogenicity...
of the proximal nail fold and the proximal nail bed can also be detected. The lateral wings of the ungual matrix may show variable degrees of thickening and decreased echogenicity as well. This condition can be uni- or bilateral, as well as, partially or entirely affects the nail plate (medial or lateral; ulnar or radial borders) (Fig. 5.7) [1, 8, 22, 23].

**Inflammatory diseases**

**Psoriasis**

This autoimmune inflammatory condition that commonly involves the skin may also affect the nail, joints, tendons, and the underlying bony margin. It has been reported that 5% of patients with nail psoriasis do not show any cutaneous involvement. Moreover, 10–20% of patients with psoriasis present with psoriatic arthritis, although patients who present with psoriatic arthritis more commonly show nail involvement (53–86%) [24, 25].

On ultrasound, psoriatic onychopathy may present with varying degrees of alterations in both the nail bed and nail plates.

These abnormalities (going from early to late phases) include (Fig. 5.8) [1, 8, 24–27]:

- thickening of the nail bed (increased distance between the ventral plate and the bony margin of the distal phalanx)
- increased blood flow within the nail bed; loss of definition of the ventral plate
- hyperechoic focal involvement of the ventral plate (which may be subclinical and usually correlates with the subungual keratosis and can be present without the involvement of the dorsal plate)
- thickening, loss of definition, and undulation of both nail plates can be detected in late phases.

On ultrasound the assessment of activity in psoriatic onychopathy can also be observed and monitored through the evaluation of blood flow (Fig. 5.9) [25]. Thus, on color Doppler ultrasound the basal activity (i.e., vascularity...
degree and sonographic anatomic changes in the nail bed) is compared with the changes detected in a follow-up examination.

Alterations in echogenicity (i.e. hypoechogenicity or heterogeneous patterns) in the distal insertion of the extensor tendons, presence of synovitis (i.e. anechoic fluid bulging from the joints with or without hypervascularity), and bony erosions (i.e. focal sites of disruption in the bony margin) can suggest a higher level of severity of the disease.

Scleroderma
Systemic sclerosis may affect both the microvascular structure and function of the nail unit. These changes
have been previously registered by other imaging modalities such as laser Doppler, thermal imaging, and nail fold capillaroscopy. Using nail fold capillaroscopy, giant capillaries, hemorrhages, and avascular areas have been described in scleroderma. Thus, vascular abnormalities are among the primary pathological components of scleroderma [28, 29].

On ultrasound, thickening and decreased echogenicity of the nail bed with upward displacement of the nail plates can be noted, which can be probably related to edema and/or chronic inflammatory changes (Fig. 5.10). Hypervascularity has been reported in the skin of the dorsum of the fingers in patients with early scleroderma, and hypovascularity may be seen in late atrophic stages in the same entity. Usually, the nail bed tends to become hypovascular in concordance with the changes in the microvascularity [1, 8].

Dermatomyositis – calcinosis
Periungual capillary changes have been described in active juvenile dermatomyositis, among them: dilated and tortuous blood vessels, areas of atrophy, telangiectases, central areas of hemorrhage, splinter hemorrhages, and bushy capillary loop formation in the proximal nail fold [30, 31].

Color Doppler ultrasound may register vascularity changes in the nail bed and also detect periungual calcinosis deposits that are frequently located in the tips of the fingers. Calcinosis appears on ultrasound as hyperechoic focal deposits frequently presenting with posterior acoustic shadowing typical of the calcium component (Fig. 5.11) [1, 8].

Lupus erythematosus
The many different types of skin lesions encountered in patients with lupus erythematosus (LE) have been classified into those that are histologically specific for LE and those that are not. While LE non-specific skin lesions on their own do not enable a diagnosis of LE, they can be essential reflections of underlying LE disease activity. The latter also applies to the involvement of the scalp and nails [31, 32].

Importantly, blood flow abnormalities that involve the digital arteries and nail bed can be detected by color Doppler ultrasound. These changes include thrombotic phenomena within the distal end of the digital arteries that can produce subsequent hypovascular changes in the nail bed, and therefore dystrophic changes in the nail bed (Fig. 5.12). Thus, variable thickness areas in the nail bed can also be observed, including thickening and thinning areas. The nail bed is
usually hypoechoic, and commonly the alterations of the echogenicity affect the ungual matrix. Secondary dystrophic abnormalities of the nail plates such as irregularities, disruption, modifications of the axis, fragmentation, and loss of the bilaminar pattern, among others, may be seen. Additionally, abnormalities in the periungual dermis such as thinning or thickening, with increased or decreased echogenicity, may be detected (Fig. 5.13) [1, 8].

**Rheumatoid arthritis**

This is a chronic progressive disorder characterized by symmetric inflammatory arthritis in association with systemic symptoms. Although considered a joint disease,
rheumatoid arthritis (RA) is associated with involvement in diverse organ systems, including the skin and nails. Clinical nail abnormalities that are commonly described associated with RA are longitudinal ridging and clubbing [33, 34].

On color Doppler ultrasound, anatomic changes in the joint, bony margins, tendons, and soft tissues can be visualized. These alterations include narrowing of the joint space, tendinosis (i.e. tendinopathy or degeneration of the fibrillar pattern of the tendon), tear or atrophy of the extensor and flexor tendons, erosions of the bony margin, periarticular and peritendinous edema, thickening decreased echogenicity, and increased blood flow in the nail bed (Fig. 5.14) [1, 8, 35].

Subungual abscesses

Periungual fistula
Infections of the nail bed may commonly be seen under immunosuppressive conditions, secondary to drugs and systemic diseases [36, 37]. Treatment may require surgical drainage; therefore, detailed presurgical provision of the anatomic extent of the collection could be necessary.

On ultrasound, fluid collections or abscesses within the nail bed appear as anechoic areas associated with thickening of the nail bed (Fig. 5.15). When air bubbles (secondary to the infectious process) are produced within the fluid collection, a hyperechoic band with reverberance
Figure 5.14  Rheumatoid arthritis. (a) Color Doppler ultrasound (longitudinal view) shows increased blood flow within the nail bed. (b) Color Doppler ultrasound (longitudinal view) shows increased periarticular blood flow in the proximal interphalangeal joint of the same finger associated with pannus and erosions. e, erosion; mph, middle phalanx; p, pannus; pip, proximal interphalangeal joint; pph, proximal phalanx.

Figure 5.15  Subungual abscess. (a) Clinical photograph. (b) Ultrasound (longitudinal view) shows 5.5 × 0.9 mm anechoic fluid collection (between markers) at the proximal part of the nail bed. (c) Three-dimensional ultrasound reconstruction demonstrates subungual anechoic fluid collection (*) underneath the nail plate.
and posterior acoustic shadowing may be seen. Free air can be displaced within the nail bed according to changes in the position of the fingernails, but usually, air bubbles maintain their top location (Fig. 5.16). Moreover, periungual infective fistulous tracts within the soft tissues can directly connect to the bony margin, nail bed, or matrix region [38]. If this occurs in the matrix region thickening and decreased echogenicity can be seen in the affected areas as a result of the inflammatory process; therefore, secondary nail dystrophy can be explained anatomically (Fig. 5.17) [1, 8].

Trauma, foreign bodies, and median canaliform nail dystrophy

Nail bed and fingertip injuries are commonly seen in emergency departments, with subungual hematomas being the most common injury to the distal part of the dorsum of the finger [39–41]. Among the structures of the nail unit, the ungual matrix is one of the most sensitive to trauma [3]; therefore, prompt diagnosis may decrease the possibility of long-term cosmetic sequelae such as nail dystrophy. Traumatic entities include foreign bodies that may be embedded in the nail bed. There are different types of materials that can be found in the nail bed, secondary both to traumatic events or, for example, to the abnormal displacement of surgical materials used for correcting the axis of toenails.

Also related to trauma is the median canaliform nail dystrophy that typically appears as a central nail groove, beginning at or distal to the proximal nail fold, from which small lateral fissures may be found. Although the onset of this nail dystrophy has occasionally been associated with either prior local trauma or the initiation of some medical treatment [42], a familial link to this entity has also been reported [43].

On ultrasound, subungual hematomas appear as anechoic fluid collections that may be associated with thickened and decreased echogenicity within the nail bed [1, 8]. Usually, in the presence of incised or penetrating wounds, the path of the injury may be recognized on ultrasound as a hypoechoic linear band. Thus, the involvement of the matrix region is assessed. Moreover, splinters of wood, pieces of glass, or metal can be recognized on ultrasound as laminar or bilaminar hyperechoic structures within the nail bed. Glass and metal may be associated with a reverberance artifact. Moreover, implants sometimes used in corrective surgery can be seen as echoic bands attached to the bony margin. Furthermore, occasionally these bands can be torn and may be displaced; therefore, they become embedded in the nail bed and produce secondary inflammatory
changes (Fig. 5.18). Ultrasound may support the diagnosis and provide the exact location of the foreign body, which can help to decide the incision site and perform imaging-guided removal [1, 8].

On ultrasound, median canalicular nail dystrophy shows as a thinning of the central proximal nail bed involving the matrix region, which suggests scarring and chronic inflammatory changes. Distally, the nail plates present thickening, loss of definition, discontinuity, and irregularities following the same path as the central proximal nail bed alteration. Usually, the nail bed tends to be hypovascular in the affected region on color Doppler ultrasound (Fig. 5.19) [1, 8].

**Cosmetic alterations**

**Implants: acrylic nails**

Artificial acrylic nails have recently become fashionable to strengthen and lengthen nails [44]. Difficulties in measuring pulse oximetry and the occurrence of contact dermatitis in patients using this cosmetic material have been reported in the literature [44–46].

On ultrasound, acrylic can be identified and separated from the nail plates as it shows as a hyperechoic linear deposit over the dorsal plate [6]. Sometimes hyperechoic spots may also be detected between the acrylic and the dorsal nail plate, probably corresponding to the glue that is used to attach the cosmetic implant to the surface of the nail (Fig. 5.20). In the presence of adverse reactions to acrylic, alterations in the echogenicity and thickness of the nail bed may be found [1, 8].

**Benign tumors and pseudotumors**

Tumoral and pseudotumoral entities may affect the nail unit and commonly can pose diagnostic challenges. These difficulties in the diagnosis may be secondary to the complex anatomy of the nail unit or masking of the nail plates and periungual tissues [47, 48].

Thus, among the significant advantages of the ultrasound technique for studying tumors of the nail are the ability to efficiently and non-invasively penetrate the nail bed from the surface to the bony margin. Ultrasound can detect tumors of a variable spectrum of sizes that can range from tiny lesions in the submillimeter range to large tumors that can measure many centimeters. The capability to distinguish small tumors is currently limited with other imaging modalities commonly used,
Figure 5.18 Subungual foreign body. (a) Clinical photograph of a patient presenting with a history of corrective surgery in the foot. Following surgery there is swelling and erythema of the fourth toe with thickening and pigmentation of the ungual region. Courtesy of P. Valdes. (b) Ultrasound (longitudinal view) shows two fragments of a foreign material (*) that corresponds to a polymer fiber (fiber tape) following the bony margin of the dorsum of the distal and middle phalanx. The fragment distally located is impinging on the nail bed, including the matrix region. The nail bed and nail plates are thickened. (c) Three-dimensional ultrasound (longitudinal view) reconstruction performed in the same case. dip, distal interphalangeal joint; dph, distal phalanx; nb, nail bed; pl, plates; pnf, proximal nail fold.

Figure 5.19 Median canalicular nail dystrophy. (a) Clinical photograph. (b) Ultrasound (longitudinal view) shows thinning of the proximal nail bed (between markers), thickening and irregularity of the dorsal plate, and loss of definition of the ventral plate in the proximal nail bed. (c) Ultrasound (transverse view) at the level of the distal nail bed demonstrates a discontinuity of the nail plates in the middle third (arrow). dph, distal phalanx; nb, nail bed; pl, plates; pnf, proximal nail fold.
Ultrasound and Other Imaging Methods

such as the currently commercially available units of CT and MRI that usually use reconstruction algorithms, which can present difficulties for detecting tumors of the nail that measure less than 3 mm [49].

In fact, ultrasound provides information on a number of characteristics of tumors that are otherwise unavailable before surgery [48]. These include:

- the origin of the lesion (ungual or periungual)
- the exact location (proximal or distal nail bed; ulnar, radial, medial, or lateral aspects of the nail unit; central or eccentric position)
- involvement of the nail unit components and surrounding structures
- the size (in every axis)
- the composition (solid, cystic)
- the blood flow (hypo- or hypervascular).

A classification of the tumors of the nail can be performed according to their origin (ungual and periungual) and nature (solid or cystic) as follows.

**Ungual origin**

**Solid**

*Glomus tumors*

These benign subungual tumors that arise from the neuromyoarterial plexus can be difficult to excise because of their usually small size. Relatively high rates of recurrence (up to 20% of cases) have been reported in patients without presurgical ultrasound [50]. Ultrasound has been used to support diagnosis and to predict with high correlation intraoperative sizes, including tumors that measure <1 mm, and exact location. The recurrence rates of glomus tumors after presurgical ultrasound have been reported to be very low in comparison with tumors without presurgical imaging [48].

On color Doppler ultrasound, glomus tumors usually appear as a well-defined hypoechoic solid subungual nodule, with increased vascularity and scalloping of the underlying bony margin of the distal phalanx. Variable peak arterial systolic velocities may be detected within the intratumoral vessels that have been reported to be as low as 3.7 cm/s and as high as 26.1 cm/s [1, 8, 50–52], the latter exceeding the peak systolic velocity that has been described for the normal posterior tibial artery (16 ± 10 cm/s) [53]. However, some histological variants of glomus tumors such as glomangiomyomas may be hypovascular. Secondary remodeling of the bony margin of the distal phalanx beneath the tumor probably reflects the slow growth pattern of the mass. Proximal locations of glomus tumors are sonographically described as more frequent than distal ones [1, 8, 48]. Therefore, presurgical knowledge of the location, nature, and diameter of the tumor may aid the choice of the incision site and size (Figs 5.21, 5.22; Videos 5.2–5.4) [50].

**Fibrous tumors**

Fibrous tumors represent diverse entities and histological subtypes that go from congenital in the case of periungual fibromas (Koenen’s tumors), usually associated with tuberous sclerosis, to acquired tumors, such as garlic clove-shaped fibromas [1, 8, 54].

On ultrasound, fibromas present a uniform hypoechoic nodular or oval structure. Their location is commonly eccentric within the nail bed, and they may affect the matrix region including one of its wings. These tumors can present variable sizes, and usually, in large tumors, a remodeling of the bony margin can be detected. Moreover, fibrous tumors may secondarily involve the lateral nail fold going from the dorsal aspect to the ventral aspect and attaching to the corresponding flexor sheath. On color Doppler ultrasound, fibrous tumors are usually hypovascular, except angiofibromas, which may present small size vascular bundles with low-velocity arterial and venous blood flow within the tumoral lesion (Figs 5.23, 5.24) [1, 8, 48].
Figure 5.21 Glomus tumor proximally located. (a) Clinical photograph. (b) Ultrasound (grayscale; longitudinal view) shows a 5.9 × 2.7 mm hypoechoic well-defined nodule (+, between markers) in the proximal nail bed. Remodeling of the bony margin of the distal phalanx is detected underlying the nodule. Loss of the bilaminar pattern and irregularities in the nail plate are demonstrated. (c) Color Doppler ultrasound shows increased blood flow (in color) within the tumor. (d) Three-dimensional power angio-ultrasound reconstruction (longitudinal view) of the nail demonstrates increased vascularity in the glomus tumor region.
Figure 5.22  Glomus tumor distally located. (a) Ultrasound (longitudinal view) shows a hypoechoic nodule (*) in the distal nail bed that also affects the hyponychium. (b) Color Doppler ultrasound (longitudinal view) demonstrates increased blood flow (in color) within the nodule. (c) The tumor (*) in three-dimensional ultrasound (longitudinal view). dph, distal phalanx; nb, nail bed; pl, plates; pnf, proximal nail fold.

Figure 5.23  Angiofibroma. (a) Clinical photograph, (b) Ultrasound (longitudinal view) shows a hypoechoic mass (*) occupying the dorsum of the nail and also extending to the nail bed. (c) Color Doppler ultrasound (longitudinal view) shows vessels (in color) within the mass (*). (d) The tumor at surgery. Courtesy of R. Soto. dip, distal interphalangeal joint; dph, distal phalanx; pnf, proximal nail fold.
Onychomatricoma

These unusual benign tumors of the nail matrix are clinically characterized by the development of longitudinal thick yellow bands in the nail plate accompanied by increased nail transverse convexity and splinter hemorrhages [55–57]. On ultrasound, they usually present an eccentric location in the nail bed and affect one of the matrix wings. Hyperechoic linear dots are described within the hypoechoic tumor that also sends projections into the interplate space and matrix region. So far, remodeling or erosive changes in the bony margin, hypervascularity, or extension into the proximal nail fold have not been reported [1, 8, 48, 58] in this type of tumor (Fig. 5.25).

Neurogenic tumors

Perineurioma. These benign tumors are derived from neural tissue, and their ungual location is extremely rare. They are different from most other common neurogenic tumors such as schwannomas or neurofibromas, and perineuriomas can be distinguished by their positive immunoreactivity for epithelial membrane antigen and lack of reactivity for S-100 protein and \( \alpha \)-smooth muscle actin. Clinically they appear as swelling, clubbing, or dystrophy of the nail and may mimic other tumoral entities such as fibrous tumors or subungual exostoses.

On ultrasound, a poorly defined hypoechoic eccentric mass has been reported. Perineurioma may involve the matrix region, especially one of the wings, and the ipsilateral nail fold. On color Doppler they present as a hypovascular tumor. Remodeling of the bony margin has not been described, although this finding could be hypothetically present in larger tumors. Neither involvement of the interplate space nor hyperechoic dots within perineuriomas has been reported (Fig. 5.26) [1, 8, 59].

Schwannoma. Subungual schwannomas are sporadic, and only four cases have been reported in the literature. Two of them were identified with ultrasound: one with grayscale ultrasound and the other with color Doppler ultrasound [60]. These tumors are composed of a proliferation of Schwann cells and show a positive S-100 immunohistochemical test.

Figure 5.24 Fibroma. (a) Clinical photograph. Courtesy of R. Soto. (b) Ultrasound (transverse view) shows an eccentric hypoechoic mass (*) that involves the nail bed and lateral nail fold, also extending through the ulnar aspect of the finger to the flexor surface. (c) The tumor outlined. (d) Ultrasound (longitudinal view) shows the contact between the mass (*) and the distal insertion of the flexor tendon (ft). dip, distal interphalangeal joint; dph, distal phalanx; lnf, lateral nail fold; nb, nail bed; pl, plates.
Ultrasound and Other Imaging Methods

On ultrasound, they present as an ill-defined hypoechoic subungual structure that remodels the bony margin of the distal phalanx and displaces the nail plate upward. A central anechoic area may be detected due to cystic degeneration. Low-flow arterial and venous vessels can be observed within the tumor, predominantly in the periphery [61].

Keratoacanthoma

Subungual keratoacanthoma is a rare benign tumor that consists of a localized proliferation of squamous epithelium with a characteristic central keratin-filled crater [62]. This tumor may not show spontaneous regression and sometimes grows progressively, therefore resulting in remodeling or erosion of the distal phalanx bony margins. All these characteristics can make it difficult to differentiate from digital squamous cell carcinoma [63].

On ultrasound, a well-circumscribed and eccentric mass with mixed echogenicity (anechoic–hypoechoic), cortical remodeling, or erosion of the bony margins, as well as being associated with posterior acoustic enhancement, has been described. The center of the tumor usually presents lower echogenicity than the rim (Fig. 5.27) [64, 65].

Pseudotumors

Ungual: solid

Granulomas. These pseudotumors are the result of extensive and chronic inflammatory changes in the nail bed. Thus, this proliferative scarring and fibrous reaction causes a mass-like effect and may secondarily involve the nail plates and the ungual matrix. A telangiectatic variant has been reported to be present in up to 9% of cases, usually presenting local tenderness and easy bleeding.

On ultrasound, granulomas appear as poorly defined hypoechoic structures that displace the nail plate and enlarge the nail bed. One or both layers of the nail plate can be thickened and present a wavy shape. Variable degrees of blood flow can be detected within granulomas going from hypovascularity to hypervascularity (telangiectatic variant) (Figs 5.28, 5.29; Video 5.5) [1, 8, 48].

Subungual warts. These lesions are proliferative fibroepithelial responses to the infection by the human papillomavirus. Subungual warts usually start on the
hyponychium and slowly grow toward the nail bed. They may cause elevation and dystrophy of the nail plates, and secondarily spread across the whole nail bed and lateral folds [1, 8, 48].

On ultrasound, they show as eccentric hypoechoic fusiform structures associated with thickening of the nail plates and interplate spaces. This sonographic appearance is similar to that previously described for plantar warts [66, 67]. Occasionally, when they are located in the proximal nail bed, subungual warts may present a nodular shape and secondary thickening of the nail plates in the same axis. On color Doppler, subungual warts are frequently hypovascular, but occasionally they may be associated with hypervascularity of the underlying dermis (Fig. 5.30) [1, 8].

**Ungual: cystic**

**Mucous cysts.** Also called mucinous cysts, these are filled with degenerated collagen and viscous mucoid fluid. Clinically, they may show as indolent nodules or swelling of the nail and periungual tissues, and when the nail matrix is compressed, they can cause dystrophic changes in the nail plates. Histology usually performs differentiation between mucous and myxoid cysts. Mucous cysts do not commonly connect to the distal interphalangeal joint.

On ultrasound, they appear as round anechoic structures sometimes with inner echoes that suggest viscous debris. Irregularities or thickening of the nail plates may be detected as signs of secondary dystrophy. Moreover, the nail plates may be displaced upward by the mass effect of the cyst. Also, mucous cysts frequently produce posterior acoustic enhancement, a sonographic artifact commonly detected in cystic lesions. On color Doppler, these cysts frequently show a lack of vascularity [1, 8, 48, 68] (Fig. 5.31).

**Periungual**

**Subungual exostoses.** These are composed of outgrowths of normal bone and/or calcified cartilaginous tissue. Subungual exostoses are more common on the feet, particularly in the great toe, and, clinically, they may produce

---

Figure 5.26 Perineurioma. (a) Ultrasound (longitudinal view) shows a hypoechoic mass (*) occupying the nail bed including the matrix region and displacing upward the nail plates (arrow). (b) The tumor (*) outlined in longitudinal view. (c) Ultrasound (transverse view) shows the eccentric location of the hypoechoic mass (*) within the nail bed affecting also the lateral nail fold. (d) The tumor outlined in transverse view. dph, distal phalanx; nb, nail bed; pl, plates; pnf, proximal nail fold.
Ultrasound and Other Imaging Methods

161
elevation and deformity of the nail plates and be associated with inflammatory changes. Often, these subungual exostoses show challenging clinical presentations, and may easily mimic subungual tumors or onychomycosis.

On ultrasound, subungual exostoses appear as linear or band-like hyperechoic structures with posterior acoustic shadowing artifact; the latter artifact is frequently seen and depends on the reflective properties of the calcium component. These exostoses usually connect with their origin in the hyperechoic line of the bony margin of the distal phalanx. When they are associated with cartilaginous tissue (osteochondroma), a hypoechoic cap may be detected surrounding the calcified hyperechoic component. Also, the hypoechoic ill-defined tissue may be seen in the periphery of the exostoses as part of a secondary inflammatory and scarring reaction (Fig. 5.32; Video 5.6) [1, 8, 48].

Periungual pyogenic granulomas. Also called periungual telangiectatic granulomas, these reactive pseudotumors are histologically similar to those previously mentioned in the subungual region. Nevertheless, when they are located in the periungual region, they tend to present more complications such as bleeding due to their direct exposure to trauma and sometimes they are clinically described as a bleeding nodule [69].

On ultrasound, they show as round or oval-shaped hypoechoic lesions that affect the dermis and subcutaneous tissue of the proximal or lateral nail folds. On color Doppler, they usually present intense vascularity; however, in cases with small size (capillary) low-velocity vessels, they may show as hypovascular lesions (Fig. 5.33) [1, 8, 48].

Periungual fibrokeratomas. These proliferative and benign fibrous tumors that lie over the nail plates
can connect with the proximal or lateral nail folds [70] and involve the ungual matrix and nail bed in the same axis.

On ultrasound, they show as hypoechoic structures that are usually hypovascular on color Doppler. Thus, periungual fibrokeratomas are eccentrically located and frequently cover one of the aspects of the nail plates. Assessment of their extension into the proximal or lateral nail folds, nail matrix, or nail bed can be provided and measured. Moreover, occasionally, these tumors may elicit remodeling of the bony margin of the distal phalanx (Fig. 5.34) [1, 8].

Cystic Myxoid cysts. These cystic lesions are commonly connected to the distal interphalangeal joint and extend...
Figure 5.29 Telangiectatic granuloma. (a) Clinical photograph. (b) Color Doppler ultrasound (longitudinal view) shows thickening, decreased echogenicity, and high hypervascularity within the nail bed that involves the matrix region. Loss of the distal part, upward displacement, as well as irregularities and wavy shape of the proximal part of the nail plate are also detected.

Figure 5.30 Subungual warts. (a) Ultrasound (longitudinal view) shows a hypoechoic fusiform subungual image (*) beneath the distal part of the nail plates. (b) Ultrasound (transverse view) of the same case as in (a) demonstrates the eccentric hypoechoic subungual image (W) that corresponds to the wart, also affecting the lateral nail fold (lnf). (c) Ultrasound (transverse view) in another case shows a larger involvement of the lateral nail fold and lateral aspect of the nail bed by a subungual wart (W, between markers). (d) Three-dimensional reconstruction (transverse view) demonstrating the same case as in (c). dph, distal nail bed; nb, nail bed; pl, plates; pnf proximal nail fold; W, wart.
into the periungual or ungual regions. Myxoid, also called synovial, cysts are frequently found in elderly patients, and are usually associated with osteoarthrosis of the distal interphalangeal joint. Thus, inflammation and leakage of synovial fluid and a hypertrophic synovial membrane can protrude into the proximal nail fold. These cystic structures may also extend into the nail bed and secondarily compress the ungual matrix directly. However, these cysts most commonly produce an extrinsic compression of the matrix from the proximal nail fold.

On ultrasound, they show as a round or oval-shaped anechoic structure located in the proximal nail fold that produces posterior acoustic reinforcement and lack of inner blood flow. Extension of the synovial cyst into the nail bed and a tortuous anechoic connecting tract with the distal interphalangeal joint may be assessed. Irregularities and deformation of the nail plate are commonly found in the same axis of the cyst due to compression of the matrix region. Osteophytes of the distal interphalangeal joint appear as hyperechoic proliferations of the bony margin and synovitis that shows as anechoic fluid is bulging from the joint are commonly detected (Fig. 5.35; Video 5.7) [1, 8, 48].

Malignant pathology

Melanoma

Subungual melanoma is uncommon, and early detection of melanoma is difficult on ultrasound since the limitations of this method include the lack of detection of pigments, in situ neoplastic lesions, or entities that measure <0.1 mm. Nevertheless, in some cases blood flow abnormalities may be detected as, for example, focal hypervascularity and/or ill-defined hypoechogenicity in the underlying lesional area (Figs 5.36, 5.37; Video 5.8). In late phases, a well-defined hypoechoic solid mass can be delimited. Erosion of the bony margin of the distal phalanx may be found underlying the tumor [71]. Ultrasound can also be used as a supporting tool in cases of congenital and longitudinal melanonychias that undergo monitoring ultrasound examinations to rule out the development of well-defined malignant masses and avoid the complications that could arise from serial biopsies [1, 8].

Squamous cell carcinoma

This malignant entity is more frequent on the fingernails and is rarely reported on the toes [72]. As previously described for melanoma, detection of in situ squamous cell carcinoma (Bowen disease) in ungual locations is also tricky on ultrasound, although at late stages a hypoechoic ill-defined solid mass can be detected. Also, destructive changes in the bony margin should be ruled out. Similar to their presentation in other corporal locations, subungual squamous cell carcinomas may present localized hypervascularity on color Doppler ultrasound, which can be a sign of malignancy (Fig. 5.38; Video 5.9) [1, 8].
Figure 5.32 Subungual exostosis. Two exostosis cases affecting the left great toe with different clinical presentations. (a) Clinical photograph of case 1. Tests for onychomycosis had been negative for more than 8 months. (b) Ultrasound (longitudinal view; comparison side by side) shows a hyperechoic band (*) within the nail bed of the left hallux that presents a posterior acoustic shadowing artifact (arrowheads). The right hallux is unremarkable. (c) Three-dimensional reconstruction (transverse view) shows a hyperechoic band (*) that emerges from the medial aspect of the bony margin of the distal phalanx. (d) Clinical photograph of case 2. (e) Right to left ultrasound comparison (grayscale; longitudinal view) demonstrates a hyperechoic band coming from the bony margin of the distal phalanx on the left side. (f) Three-dimensional reconstruction of the exostosis shown in case 2. dph, distal phalanx; nb, nail bed; pl, nail plates; pnf, proximal nail fold.
Figure 5.33 Periungual pyogenic (telangiectatic) granuloma. (a) Clinical photograph. (b) Ultrasound (longitudinal view) shows a hypoechoic round mass (\(\ast\), between markers) in the proximal nail fold. (c) Three-dimensional reconstruction of the same mass (\(\ast\)). (d) The mass at surgery. Courtesy of R. Soto. dph, distal phalanx; nb, nail bed; pl, plates.

Figure 5.34 Periungual fibroma. (a) Clinical photograph. (b) Ultrasound (longitudinal view) shows a hypoechoic structure (\(\ast\)) that involves the periungual lateral nail fold but also extends deeper into the proximal nail bed. The lateral aspect of the bony margin of the distal phalanx presents a remodeling (arrow). dip, distal interphalangeal joint; dph, distal phalanx; pnf, proximal nail fold.
Figure 5.35 Myxoid (synovial) cyst. Two cases showing myxoid cysts. (a) Clinical photograph of case 1. (b) Ultrasound (longitudinal view) shows an anechoic rounded cyst (\(\ast\), between markers) in the proximal nail fold compressing the matrix region. A connecting anechoic tract to the distal interphalangeal joint is detected (arrow). (c) Color Doppler ultrasound (longitudinal view) shows a small arterial vessel in the periphery of the cyst but absent blood flow within the lesion. (d) Clinical photograph of case 2. (e) Grayscale and (f) three-dimensional reconstruction ultrasound (longitudinal view) demonstrate an oval-shaped anechoic structure in the proximal nail fold compressing the proximal part of the nail bed. dip, distal interphalangeal joint; dph, distal phalanx; et, extensor tendon; m, matrix region; nb, nail bed; pl, plates.

Figure 5.36 Melanoma in situ. (a) Clinical photograph. (b) Ultrasound (longitudinal view) shows localized hypervascularity in the ulnar aspect of the finger (lesion location) in comparison with the radial aspect that presents normal blood flow. Notice that no nodule or mass is detected within the nail bed. nb, nail bed; pnf, proximal nail fold.
Conclusion

Ultrasound imaging of the nail can be a powerful tool in daily practice and can provide detailed anatomic data on their nature (solid or cystic), exact location, diameters in all axes, ungual and periungual involvement, blood flow patterns, activity, and severity in a wide range of common nail conditions.

OPTICAL COHERENCE TOMOGRAPHY
Gregor B.E. Jemec

Introduction

Imaging is often rightfully accompanied by an insatiable appetite for detail in which naked eye inspection is replaced by dermoscopy, by X-ray, or by high-frequency ultrasound. This development provides not only a greater depth of detail and more data, but generally also better information in a clinical setting. Technically it is possible to obtain images of tissue in vivo with an even greater resolution than that of high-frequency ultrasound. Commercially available light technologies based on the principles of optical coherence tomography (OCT) have been explored in order to ascertain the method’s potential in clinical medicine [73, 74].

Technology

OCT relies on the capture and amplification of reflected infrared light, and computerized data analysis that results in B (brightness) scans similar to those produced by high-frequency ultrasound equipment, albeit with a different resolution and penetration effect. The principle of OCT imaging is analogous to ultrasound, except it uses
near-infrared light impulses rather than soundwaves to produce images. OCT is based on interferometry, and the images are captured by detecting the intensity of the reflected light as a function of depth. The OCT images are usually displayed in cross-sectional (vertical) and horizontal or en-face (horizontal) views and can be either two or three dimensional. Most conventional OCT systems can attain a penetration depth of up to 1–2 mm and a resolution of <7.5 µm (lateral) and <5 µm (axial) with a 6×6 mm field of view [74]. Systems with higher resolution, described as high-definition (HD)-OCT, and various other refinements, including imaging of the microvasculature as in dynamic (D)-OCT, are available [74, 75].

Normal nail anatomy

OCT should currently be regarded as an experimental method for imaging nails, and studies are underway to define its role. The resolution is less than that for reflectance confocal microscopy, but with a penetration depth of up to 2 mm OCT appears to be suitable for imaging the nail plate, the subungal skin, and at least the superficial parts of the matrix (Fig. 5.39).

The normal architecture of the nail apparatus is easily recognized in OCT imaging [76]. In vertical imaging, the nail plate is presented as a sharply demarcated, layered homogenous gray area of the image. The use of speckle-variance OCT provides for better discrimination between the nail plate and the underlying skin [77]. As a consequence, OCT has been used to study nail plate thickness in vivo, and has been found to be more precise than high-frequency ultrasound measurements [77]. In addition to more precise estimates of thickness, OCT has also been used to describe experimentally induced changes in nail hydration [78].

In contrast, the matrix appears more hyperreflective (white) and is surrounded by a more hyporeflective layer underneath the proximal nail fold. The increased reflection seen in the distal matrix is clearly seen to continue underneath the proximal nail fold in OCT images, suggesting that it reflects tissue qualities and is not an artifact. In the en-face image mode the surface of the nail plate reveals a granular ridged structure.

Using D-OCT it is possible to image the microvasculature of the nail apparatus, including the proximal nail fold, providing a new high-resolution option for capillaroscopy (see Chapter 7) [79] (Fig. 5.40). In addition, and as a unique feature of this method, the subungal microvasculature can be visualized.

Nail pathology

Comparatively few studies have addressed the role of OCT in nail pathology. An obvious area of interest is onychomycosis. The possibility of a non-invasive tool to screen for onychomycosis holds considerable advantages over existing methods such as mycology culture or polymerase chain reaction (PCR) analysis, which may be subject to sampling error. The ability of OCT to identify fungal infection of the nail has been explored in two studies, which strongly suggest that OCT can identify a greater number of infections than nail scarping and potassium hydroxide (KOH) preparation and culture [80]. A later study compared OCT, RSM, histology, and periodic acid–Schiff staining of nail

Figure 5.39 Conventional optical coherence tomography of a normal human nail. (a) The nail plate in transverse section. (b) The proximal nail plate, showing the white (hyperreflective) matrix. (c) En-face image of the nail matrix.
biopsies with KOH and PCR. In this study OCT was found to have the second best sensitivity but a low specificity due to the limited resolution [81]. OCT may therefore be able to distinguish fungal and psoriatic changes.

Because the method is based on reflected light from the tissue, absorbing (dark) lesions generally provide little information and white lesions cast shadows onto the underlying tissue, suggestive of loss of signal intensity below the lesion. For instance, spots of posttraumatic leukonychia that appear white have a shadow effect in OCT images. The high resolution however generally increases sensitivity to structural abnormalities, showing a good correlation with careful clinical examination and even identifying abnormalities in clinically normal-appearing nails. OCT may therefore prove useful in the management of inflammatory diseases, and in specific studies of psoriatic nails OCT has been able to identify subungual abnormalities [82]. This suggests that the method has the potential to document early changes in inflammatory nail pathologies during treatment, but more confirmatory studies are needed to substantiate these claims [83]. It may further be speculated that the method is able to describe matrix changes that may predispose to nail plate abnormalities, but this is as yet unproven.

HIGH-RESOLUTION PERIPHERAL QUANTITATIVE COMPUTED TOMOGRAPHY (HR-pQCT)

Axel Villani

In addition to all the above-mentioned nail imaging devices, other tools can also be used for scientific and medical research purposes. Among those, high-resolution peripheral quantitative computed tomography (HR-pQCT), which has been commercially available since the mid-2000s, is a non-invasive, low-radiation method. It allows the assessment of bone microarchitecture and volumetric bone mineral density in cortical and trabecular compartments [84]. Currently, only one commercial HR-pQCT machine, the XtremeCT (Scanco Medical AG, Brüttisellen, Switzerland), is able to perform scans at a resolution sufficient to measure three-dimensional human bone microarchitecture in vivo (isotropic voxel size of 82 µm). It is mainly designed for clinical research and has notably been used to understand the age- and sex-related changes in bone microarchitecture, or to assess hand bone loss and erosions in early rheumatoid arthritis [85]. However, this device is not designed to assess tendons and enthesitis, but this can easily be overcome when used in combination with fast ultrasonography. Recently, Villani et al. [86] used HR-pQCT combined with ultrasonography to analyze the distal digital compartment and decipher the potential links between nail psoriasis, enthesitis, and the distal phalanx. There is indeed growing evidence to indicate that psoriatic nail disease, and more specifically onycholysis, could be a marker of deep inflammatory involvement or even a precursor of psoriatic arthritis [87, 88]: nail psoriasis would then be a clinical marker of subclinical distal enthesopathy and, by extension, of bone microstructural alterations [89]. In this study, HR-pQCT was used to analyze the bone microarchitecture underlying the nail (Fig. 5.41): patients with psoriatic onycholysis without psoriatic arthritis had a mean number of 3.6 ± 0.77 erosions of the distal interphalangeal joint compared with only 0.21 ± 0.1 in patients without any nail involvement or psoriatic arthritis (p = 0.035) [86]. Nail psoriasis was also associated with the presence of syndesmophytes. These findings support the pathogenic role of enthesopathy in joint involvement of psoriatic arthritis and underline the potential severity of onycholysis compared with isolated cutaneous psoriasis only. Nail psoriasis and especially onycholysis could be
Ultrasound and Other Imaging Methods

the clinical expression of a deep inflammation of the distal interphalangeal joint.

Since this technology is designed to specifically assess bone microarchitecture, it could be used in the field of nail diseases to detect early bone erosions (nail tumors) or to assess potential links between bone loss and nail inflammatory disorders, but this is mainly restricted to nail psoriasis and psoriatic arthritis.

References


Chapter 6

Magnetic Resonance Imaging

Jean-Luc Drapé

Introduction

Imaging of the nail apparatus has profited from recent advances in radiology. The latest generation of ultrasound probes provide very high spatial resolution (HSR) of the first few millimeters of the superficial tissues under the probe. Microcoils dedicated to magnetic resonance imaging (MRI) of the fingers are now available and offer exquisite anatomic detail of the nail apparatus. Tumors of the nail apparatus may be difficult to diagnose because of the anatomic particularities of this organ. Symptoms, growth, and above all the appearance of the tumors may be modified by the screen produced by the nail plate. Deep lesions that originate close to the nail root are covered by the posterior nail fold and may only be expressed by a nail dystrophy. Radiographs and computed tomography (CT) may detect calcifications and adjacent bone abnormalities. Ultrasonography (US) is effective to depict tumors but may be limited for tissue characterization. MRI is indicated when US findings are equivocal and provides more specific patterns of tumors.

MRI is well known for its high contrast of the soft tissues. Low-field magnetic resonance (MR) units are not adapted to image a fingertip. It has been possible to obtain HSR MR images of the nail apparatus since 1986. Since 1990, several imaging departments have inserted home-built high-resolution modules with local gradient surface coils into whole-body MRI units. When associated with the most powerful 1.5- or 3-tesla (T) whole-body MR units, recent 8-16-channel wrist or hand coils may provide clinically helpful images of the nail apparatus. However, small surface coils dedicated to finger imaging are optimum and are now available with all high-field MR units.

Constraints on magnetic resonance imaging of the nail apparatus

The nail apparatus presents a multilayered structure on axial images. A voxel height <100 µm, about the thickness of the epithelial layer of the nail bed, is necessary in the direction from the surface to the depth. Nevertheless, unlike the skin, which is a very superficial structure, the nail apparatus may require an evaluation of the deep layers of the nail bed or even of the pulp when a tumor extends under the lateral interosseous ligament. Routinely, a field of view of 2–3 cm is best to give a whole view of the nail apparatus, while maintaining an acceptable signal-to-noise (SNR) ratio.

When using a plane circular surface coil, the nail plate must be placed against the coil to offer the maximum
signal close to the superficial layers of the nail apparatus. The hand is placed with the HSR coil fixed on the center of the nail apparatus. Full cooperation of the patient and an efficient mechanical support with adhesive bandages are necessary to achieve strict immobility. The patient must be prone with the arm elevated above the head so that the finger can be placed at the center of the magnetic field, allowing excellent fat suppression sequences. Some patients with painful shoulders are not able to maintain this position throughout the examination. However, the failure ratio is very low. To study the toes, the positioning of the patient is more comfortable. The patient is prone with the foot in the gantry and the dorsal aspect of the toe against the HSR coil. In all cases, perfect immobility of the distal phalanx is necessary to avoid movement artifacts, which are particularly disturbing with HSR. For this reason, children younger than 6 years are difficult to image.

**Imaging sequences**

The sequences must be conceived to give the best compromise between HSR and a sufficient SNR. A voxel size of $117 \times 234 \times 3000 \, \mu m^3$ is obtained with a 3-cm field of view and a $256 \times 128$ matrix. A routine examination includes axial T1-weighted spin echo (SE), axial and sagittal T2-weighted SE fat-suppressed, or short time inversion recovery (STIR) images. A 3-mm slice thickness may be too large to accurately assess the nail matrix or tiny lesions and thinner slices may be mandatory. T2-weighted three-dimensional (3D) acquisitions provide 0.7–1-mm thick contiguous images. Intravenous injection of 0.1 mmol/kg gadolinium is adapted to the suspected pathology. MR angiography of the fingertip may be performed after injection with early and delayed acquisition to study the architecture of vascular malformations.

**Normal magnetic resonance appearance of the nail apparatus**

**Sagittal plane**

The sagittal images show the nail plate in its full length. The highly organized and keratinized nail plate presents a lack of signal [1, 2]. As for collagen, this scleroprotein causes dramatic shortening of the relaxation times [3]. If the ventral aspect of the nail plate is well defined by the high signal of the epidermis layer of the matrix and the nail bed, its dorsal aspect is not visible. Its interface with the air, also presenting as a lack of signal, is not detectable. Thus, the application of Vaseline to the plate before its positioning on the surface coil gives a high contrast of the dorsal aspect of the nail plate whatever the sequence used. The nail plate is very thin close to the nail root, and is surrounded by the thin high signal of the cul-de-sac of the matrix. It is not possible to highlight a different signal between that of the nail matrix and that of the epidermis layer of the nail bed or the ventral aspect of the proximal nail fold. The epidermis layer thickens more at the level of the hyponychium (Fig. 6.1). The nail plate progressively thickens towards its free edge. This finding is in agreement with Johnson’s reports on US. However, MRI is not able to distinguish the different layers of the nail plate described on histological studies. Whatever the sequence used, the plate always remains without signal throughout its thickness.

T2-weighted sagittal images show an oval-shaped area of high signal in the deep dermis beneath the nail matrix (Fig. 6.1) This structure is related to the lunula, as we have demonstrated in 40 healthy volunteers [4]. The length of this area is highly correlated to the length of the lunula. When the lunula is lacking, this dermal area is still present but does not extend past the limits of the posterior nail fold. This area presents a strong and homogeneous enhancement after injection of gadolinium and its limits are well defined. The histological studies of this area show that the dermis is more uniform, with a looser connective tissue than that of the more distal nail bed. The microvascularization presents a more regular vascular network than in the nail bed [5]. The meaning and the role of this area are still obscure. According to Baden, the matrix cells may produce some proteins under control of the underlying dermis [6, 7].

The sagittal images also accurately depict the distal interphalangeal joint with the insertion of the terminal band of the extensor tendon onto the base of the

---

**Figure 6.1** Sagittal three-dimensional 1-mm-thick T2-weighted image. 1, proximal matrix; 2, cul-de-sac; 3, distal matrix; 4, epithelial layer nail bed; 5, hyponychium; 6, cuticle; 7, nail plate; 8, Vaseline; 9, submatrical high-signal area; 10, extensor tendon; 11, cartilage; 12, joint fluid; 13, volar plate.
distal phalanx, the articular cartilage, and the palmar plate (Fig. 6.1).

**Axial plane**

The proximal axial slices easily demonstrate the proximal nail fold, the extensor and flexor digitorum tendons, the lateral ligaments of the distal interphalangeal joint, and the palmar plate (Fig. 6.2). The root of the nail plate appears surrounded by the proximal and distal matrix. The curvature of the matrix is similar to that of the nail plate (Fig. 6.3). The posterolateral borders of the nail plate are contiguous with the matricophalangeal ligaments. At the level of the distal matrix, the slice clearly shows thickening of the epidermis layer close to the median line, while the ridges are not visible. The dermis beneath the matrix presents a homogeneous high signal on T2-weighted images and after injection of gadolinium (Fig. 6.3). The lateral nail folds and the rima ungualeum, bordered by the Flint lateral interosseous ligaments, are well defined on the axial slices of the nail bed (Fig. 6.4). The epidermis layer of the nail bed presents a thin and high signal. The underlying dermis shows a thin superficial layer with low signal and a thick deep layer with a heterogeneous signal. This heterogeneity is reinforced by the injection of gadolinium, because of the numerous enhanced glomus bodies of the nail bed. These normal glomi are remarkable arteriovenous shunts, highly concentrated in the tips of the digits, particularly beneath the nails. Each glomus body is a tiny encapsulated oval organ 300 µm long. The nail beds of fingers and toes contain 93–501 glomus bodies per square centimeter [8].

**Coronal plane**

Routinely, the coronal slices are not acquired. This plane may be added in the case of a lateral or distal lesion of the fingertip. However, the different elements are often tangential to the coronal plane and therefore exposed to the partial volume artifact. The coronal plane is the plane of acquisition for MR angiography of the nail apparatus. The volumetric reformatting (maximum intensity projection; MIP) provides imaging of the whole volume of the fingertip (Fig. 6.5).
Tumors of the nail apparatus

The indications for US and MRI of the nail apparatus are still under investigation but tumor pathologies are the main indication. This chapter does not present an exhaustive imaging atlas of all the tumors of the nail apparatus. The goals of modern imaging are to confirm the clinical suspicion of a periungual tumor, to accurately assess the extension, and to note some specific patterns. Numerous types of tumors can involve the subungual space: cystic pseudotumors (mucoid pseudocyst), benign solid tumors (epithelial tumors, fibrous tumors, glomus tumors, vascular malformations, epithelial tumors, giant cell tumors of the tendon sheath, etc.), osteochondromatous tumors (subungual exostosis), and malignant tumors (squamous cell carcinoma, malignant melanoma, chondrosarcoma).

Mucoid pseudocysts

Radiographs are mandatory in suspected mucoid pseudocyst of the digits. The depiction of a distal interphalangeal joint osteoarthritis is a clue to the diagnosis. The lateral view is the best view to show the dorsal osteophytes of the head of the middle phalanx and the base of the distal phalanx in 70% of cases [9]. The soft tissues of the eponychium may be thickened (Fig. 6.6). The lateral and posteroanterior views depict the joint space narrowing and sometimes a lateral subluxation of the distal phalanx. In erosive osteoarthritis the joint space narrowing presents a seagull pattern often with a large subchondral cystic bone resorption (Fig. 6.6). In rare cases, bone scalloping of the dorsal aspect of the cortex of the distal phalanx may reveal a subungual extension (Fig. 6.6). This bone scalloping may be easily seen on oblique views.

A complementary imaging modality (US or MRI) may be helpful in doubtful clinical cases and to plan surgery. In fact, a high rate of recurrence in spite of numerous proposed treatments reinforces the need for accurate preoperative imaging. US and MRI accurately analyze the relations between the cyst and the distal interphalangeal joint.

Ultrasound shows the specific patterns of a mucoid pseudocyst with a well-defined round or multilobulated anechoic structure and a posterior enhancement (Fig. 6.7). Doppler images are negative (Fig. 6.8). With MRI, the cyst presents thin regular walls, a low signal on T1-weighted images, and very high signal on T2-weighted images (Fig. 6.9). Intracystic septa are best seen on T2-weighted images in 39% of cases. The injection of gadolinium shows an early faint peripheral enhancement, quite different from that of glomus tumors (Fig. 6.10). With time, the enhancement moves toward the center of the cyst. This “diffusion” of contrast medium may be compared to the intraarticular diffusion of gadolinium at
Magnetic Resonance Imaging

the level of the knee through the synovium after intravenous injection. However, a true synovial membrane has not been found in digital cysts, apart from a possible peduncle.

Most of the cysts are solitary and located on the proximal nail fold. However, US and MRI are able to highlight satellite cysts or sagging multiloculated cysts. These latter forms may be difficult to detect clinically, unless a typical story of swelling and discharge of a thick fluid from the proximal nail fold is found. In these infrequent forms (22%), a connection with the distal interphalangeal joint is difficult to demonstrate and may explain an in situ metaplasia of the dermis.

In most cases (82%), US or MRI highlights a peduncle connecting the cyst and the distal interphalangeal joint. Parasagittal and mainly axial views depict a lateral peduncle, beneath the insertion of the extensor digitorum tendon on the base of the distal phalanx (Fig. 6.9). T2-weighted images are indicated to show the high signal of the peduncle. When the surgical decision is made, the peduncle must be detected and tied up or removed in order to avoid the frequent recurrences. Both imaging modalities show directly the conflict between a dorsal osteophytosis of the head of the middle phalanx and the

---

**Figure 6.6** Mucoid pseudocyst. (a) Lateral radiograph shows thickening of the posterior nail fold (arrows) and severe osteoarthritis of the distal interphalangeal joint. (b) Posteroanterior view of severe erosive osteoarthritis. (c) Lateral view of a dorsal bone erosion due to a subungual mucoid cyst.

**Figure 6.7** Mucoid pseudocyst of the posterior nail fold. Sagittal ultrasonography image: (*) mucoid pseudocyst; (arrowheads) extensor tendon lifted by osteophytes (OST); (arrows) nail root. DIPJ, distal interphalangeal joint.

**Figure 6.8** Mucoid pseudocyst of the posterior nail fold and the subungual area. Sagittal ultrasonography power Doppler image: (*) mucoid pseudocyst without inner or peripheral positive Doppler. Positive Doppler of vascular elements besides the cyst. Nail root (arrows). DIPJ, distal interphalangeal joint; DP, distal phalanx.
The extensor digitorum tendon (Fig. 6.9). The tendon is lifted up, thickened or torn. The dorsal osteophyte must be removed at the same time as the cyst and the peduncle in order to avoid a recurrence. A thickening and an enhancement of the synovium of the distal interphalangeal joint is depicted in half of the cases. This hyperplasia of the synovium associated with osteophytes may contribute to Heberden’s nodes [10].

Mucoid cysts extend into the nail bed in 30% of cases. This location is poorly studied and rarely mentioned in the literature. US and MRI are able to detect this type of cyst (Figs 6.8–6.10). Symptoms may mislead by suggesting the diagnosis of a glomus tumor when the cyst is painful. When the cyst is large, erosion of the cortex of the

---

**Figure 6.9** Mucoid pseudocyst of the posterior nail fold. Sagittal (a) and axial (b,c) three-dimensional T2-weighted gradient echo images. The cyst presents a very high signal on the T2-weighted images, sharp limits, and internal septa (arrows). Note the large dorsal osteophytes of the distal interphalangeal joint lifting up the extensor tendon (small arrows). Some fluid is depicted in the dorsal recess of the joint beneath the extensor tendon (arrowheads). The pedicle (black arrows) is always on one aspect of the attachment of the extensor tendon.

**Figure 6.10** Painful subungual mucoid pseudocyst. Axial T1-weighted spin echo image before (a) and after (b) injection of gadolinium and fat saturation. Spontaneously the mass in the lateral part of the nail bed with a bone erosion may evoke a glomus tumor (*). The lack of enhancement eliminates this hypothesis.
underlying phalanx may occur in the confined space of the nail bed (Figs 6.6, 6.11). The cyst is in the dermis beneath the nail matrix, close to the distal interphalangeal joint. The matrix compression may induce a fissure of the nail plate with a claw deformity. Most often, the cyst is bilobed with a component in the proximal nail fold (Fig. 6.12) and more rarely in the pulp, associated with the nail bed component. The submatrical extension may be clinically occult and responsible for recurrence. The detection of a peduncle is crucial, since its resection may be enough to collapse the cyst and avoid direct access to the matrix.

**Epithelial tumors**

Among the epithelial tumors, we have only explored benign tumors such as periungual warts, epidermoid cysts, keratoacanthomas, and onychomatricomas.

The *warts* are induced by human papillomaviruses. They are benign fibroepithelial tumors, poorly contagious, with an irregular keratotic surface. Typically, the warts are periungual. The subungual locations, when they are painful, may mimic a glomus tumor all the more as the long-term forms sometimes induce bone erosion. Warts of the hyponychium may be subtle and go unnoticed. Histological examination may be necessary to distinguish warts from verrucous Bowen disease and even from early squamous cell carcinoma.

MRI easily estimates the thickening of the epidermis in depth and surface, particularly in the subungual area and at the level of the hyponychium. The signal is identical to that of normal epidermis on all sequences. A thick superficial layer with lack of signal may cover the thickened epidermis and corresponds to the corneal layer or to after effects of cryotherapy, laser, etc. (Fig. 6.13).

Figure 6.11 Subungual mucoid pseudocyst. Sagittal T2-weighted three-dimensional gradient echo image shows a large cyst in the nail bed with deep bone erosion of the underlying phalanx at the distal part of the cyst.

Figure 6.12 Subungual mucoid pseudocyst. (a) Sagittal T2-weighted three-dimensional gradient echo image shows a proximal part in the posterior nail fold and a distal subungual part displacing the nail root (arrows). (b) Parasagittal slice depicts the lateral pedicle (arrows).

Figure 6.13 Periungual wart. Axial three-dimensional gradient echo image at the level of the nail matrix. The wart appears as a thickening of the epidermis layer (arrows) with a signal identical to that of the nail matrix. A thick superficial layer without signal is due to the corneous layer and after effects (*).
Keratoacanthoma is a rare, benign, but rapidly growing tumor located in the most distal part of the nail bed. The lesion may start as a small and painful keratotic nodule beneath the free edge. Spontaneous regression is rare in subungual locations [11].

A crescent-shaped bony erosion of the distal phalanx may be depicted on radiographs. There is no bone sclerosis or periostal reaction. However, US or MRI better demonstrate the bony erosion and a deep infiltrating lesion of the distal nail bed (Fig. 6.14). MR images usually show a large bony destruction by a nodule with a homogeneous signal (intermediate signal on T1-weighted images and high signal on T2-weighted images). In some cases, a central area of low signal indicates a central plug of horny material filling the crater, but this is inconsistent (Fig. 6.14). The limits may be ill defined with edema in the surrounding tissues.

Keratoacanthoma and squamous cell carcinoma present some similarities and cannot be differentiated with imaging. However, subungual squamous cell carcinoma occurs in older patients, grows more slowly, and may mimic chronic inflammation [12]. Histology is mandatory and shows more aggressive histological patterns.

Keratin cysts

Implantation epidermoid cysts of the distal phalanx are rare, usually secondary to trauma with implantation of epidermis into subcutaneous tissue or even into bone. An old trauma often goes unnoticed. The cyst may develop on a scar after surgery. The phalanx progressively expands and clubbing becomes obvious.

Early in the disease, bone erosion is absent or subtle and is not visible on radiographs but may be depicted with US or MRI. The bone erosion of the distal phalanx is a round, precisely rimmed erosion without septa or peripheral sclerosis (Fig. 6.15). Radiographs may reveal a pathological fracture, calcifications, or ossifications (Fig. 6.16). MRI shows a regular mass with slightly heterogeneous content of low to high signal on T1- and T2-weighted images. The low-signal component on T2-weighted images is evocative, particularly in the case of a whorled pattern of keratin layers (onion-ring appearance) (Fig. 6.17). A heterogeneous enhancement is noted after injection of gadolinium whereas orthokeratin content does not enhance [13]. The thin epidermal layer is depicted as a regular rim with a high signal identical to that of normal epidermis (Fig. 6.18). The bone erosions, even subtle, are highly detected on axial images. The area of an old penetrating injury may be marked by magnetic susceptibility artifacts of very low signal on gradient echo images (Fig. 6.19). Ruptured cysts present a thicker and more irregular peripheral enhancement with edema of the nail bed [14].

Histology shows a simple epidermoid cyst filled with orthokeratin and lined with a thin layer of epidermis.

The onychomatricomas were first described by Baran and Klint [15] as a filamentous tufted tumor in the matrix of a funnel-shaped nail. In cases of non-conclusive clinical examination, US and MRI may confirm the diagnosis. Sagittal images are essential to highlight the tumoral...

Figure 6.14 Keratoacanthoma (arrows). Magnetic resonance sagittal gradient echo image after injection of gadolinium. Note the osteolysis of the distal phalanx (arrowhead).

Figure 6.15 Subungual keratin cyst. Well-defined bone erosion of the dorsal cortex of the phalanx.

Figure 6.16 Calcifying keratin cyst. The calcifications are in the area involving the posterior nail fold (arrows). Large bone erosion (arrowheads) due to the subungual extension.
epithelial proliferation in the matrical area as a well-defined nodule. The center shows low signal on all images with a peripheral rim with a signal identical to that of normal epidermis. The lesion expands distally with filamentous extensions spreading into the funnel-shaped nail plate (Fig. 6.20). They present a higher signal on T2-weighted images due to a mucoid stroma with high water content. Axial slices accurately show the holes in the substance of the nail plate, filled with the filamentous extensions. The nail plate may be strongly thickened with a deformity of the underlying nail bed (Fig. 6.21). On the toes the onychomatricoma is more laterally located. The epithelial proliferation is less visible and the filamentous extensions are often numerous but smaller (Fig. 6.22).

Figure 6.17 Subungual keratin cyst. (a) Sagittal T2-weighted gradient echo: well-defined cyst developed beneath the nail matrix with a peripheral intermediate signal (arrowheads) and central layers of low signal with an onion-ring appearance (*). (b) Axial T2-weighted gradient echo image: the cyst(*) invades the distal phalanx (arrows) and interrupts the lateral third of the nail root and matrix (arrowheads).

Figure 6.18 Subungual keratin cyst. (a) Coronal power Doppler image shows the lateral hypoechoic cyst (arrows) with faint peripheral positive Doppler. (b) Coronal postenhanced T1-weighted spin echo image with a poor central enhancement (*) and an epithelium wall (arrows). Bone erosion (arrowhead).

Figure 6.19 Keratin cyst. Axial postenhanced fat saturation T1-weighted image depicts a large subungual cyst with a peripheral epidermis layer (arrows) with a bony invasion (*). Artifact due to a previous penetrating trauma (arrowhead).
Numerous fibrous tumors can develop beneath and around the nail plate. These tumors, ranging from dermatofibromas to digital fibrokeratomas, present a wide range of clinical patterns despite a relative histological uniformity. In fact, Koenen’s tumor, acquired fibrokeratoma, and dermatofibroma present some “clinical continuity.”

Acquired periungual fibrokeratomas

Most emerge from the proximal nail fold and grow in a splint of the nail plate, but some may be multiple and beneath the nail plate [16]. MRI accurately depicts the emerging component and generally highlights the deep implantation close to the nail root. The signal of the tumor depends on the different histological types: very low signal on all sequences for the dense and numerous collagen bundle type, and high signal on T2-weighted images in cases of mucoid stroma. Intralesional septa and the acanthotic epidermal coverage show regular limits and a signal identical to that of normal epidermis (Fig. 6.23). MRI is also able to depict a tumor involving the ventral aspect of the proximal nail fold with an epithelial invagination.
Fibromas, knuckle pads

Radiographs may depict bone erosion and thickening of the soft tissues. There are no calcifications. MRI findings are suggestive with a mainly low-signal nodule on all sequences and very dark irregular areas of extremely dense connective bundles (Fig. 6.24). These patterns and the lack of an obvious peripheral rim differentiate them from acquired fibrokeratomas. A faint and heterogeneous uptake of contrast medium may be noted.

Vascular tumors

Glomus tumors

Glomus tumors are a main indication for US or MRI of the nail apparatus. The classic triad associating pain, painful point, and cold sensitivity is evocative but rather infrequent. The lack of pain provoked by coldness may occur in 23% of cases [17]. The mean diagnostic delay is quite long and varies from 4 to 7 years in the literature [18]. Up to 75% of glomus tumors occur in the hand, and approximately 65% of these are in the fingertips, particularly the subungual space [19].

Radiographs are poorly sensitive to depict a slight bone erosion of the distal phalanx or an abnormal thickening of the nail bed (Fig. 6.25). US or MRI are highly accurate imaging modalities to highlight tiny lesions as small as 1.5 mm. HSR is necessary with both techniques. MRI is
able to depict normal glomus bodies with T2-weighted images and after injection of gadolinium.

Tumor signal may be equivocal and some studies in the literature report conflicting signal behavior. Although most of the tumors present a high signal on T2-weighted images, on T1-weighted images the lesions could present a low signal (Fig. 6.26) [20], a high signal (hemorrhage or vascular component?) [21], or an intermediate or heterogeneous signal with a tumoral core [22]. MRI may be negative in 10% of cases and therefore a negative result does not rule out the diagnosis [23]. However, the accuracy of MRI is dependent on the technical management of the examination (the coil used, sequences, MR angiography). Negative MRI may be secondary to atypical pathology (glomangioma, glomangiomyoma, glomangiopericytoma, symplastic glomus tumors) [24].

In fact, the signal behavior depends on the histological composition. Glomus tumors are the result of hyperplasia of one or several elements of the glomus bodies and may be considered hamartomas. Masson [25] described different histological variants. They are not routinely mentioned in pathological reports, as they have no prognostic significance. However, it is important to understand their involvement in the tumor signal [26].

The vascular type is composed of numerous vascular lumina. Doppler ultrasound images show numerous intrallesional positive pixels (Fig. 6.27) [27]. However, almost 60% of tumors present only little or no significant internal blood flow, with 12% being misdiagnosed [28]. On MR images, the enhancement is very high after injection of gadolinium and the signal is also elevated on T2-weighted images (Figs 6.27, 6.28). The cellular or solid type mainly presents a proliferation of epithelioid cells (glomus cells) and a relative paucity of vascular lumina. This type of tumor is quite difficult to detect with US and MRI. The contrast between the normal dermis of the nail bed...
Magnetic Resonance Imaging

The tumor enhances early at the arterial phase with uptake on the delayed phases (Fig. 6.29). Thin 3D contiguous gradient echo slices may also be helpful and are the most appropriate to depict a peripheral capsule or a slight bone erosion on the dorsal aspect of the distal phalanx (Fig. 6.30). The mucoid type with a mucoid degeneration of the stroma presents a faint enhancement but a very high signal on T2-weighted images due to the large amount of water in the stroma. Numerous tumors are a combination of these three features (Fig. 6.31).

Most often, the tumor limits are well defined, with a peripheral pseudocapsule in nearly 25% of cases. This capsule is a reaction by the surrounding connective tissue. It presents a very low signal on all sequences, but is more visible on T2-weighted images or 3D gradient echo images (Figs 6.28, 6.30). Its analysis is greatly facilitated by high-resolution MRI. When the tumor limits are ill defined, the injection of gadolinium may depict small tumor foci extending in the nearby nail bed (satellite or “skip” lesions) [29]. Often in these cases, some adhesions with the nail bed are noted during surgery (Fig. 6.32). Local invasion of the capsule is debated and was reported on histological examinations in 1–2% of cases by Kohout and Stout [30] but was not found by Carroll and Bermann [31]. It is certain that the risk of recurrence is high if tumoral tissue is left in situ during surgery of these ill-defined lesions. The recurrence rate varies from 12% to 24% in the literature. MRI appears particularly helpful in cases of recurrent pain because it helps distinguish between postsurgical pain and pain due to residual or recurrent glomus tumor after surgery (Fig. 6.33). MRI is also able to depict multiple glomus tumors in the same fingertip. In these cases, the tumors are usually close and one of them may be missed during surgery without previous imaging (Fig. 6.32). MRI is essential in these cases to plan the surgical approach.

In most cases, the tumor is located in the subungual area, in the supporting tissue of the nail bed or the matrix. Usually, the lesion is deep, close to the periosteum of the underlying phalanx. Often, a cortical erosion is depicted on axial ultrasound or MR images, although it is occult on radiographs (Figs 6.26, 6.27, 6.30). These axial slices are essential to distinguish the tumors on the median line from those of the lateral part of the nail bed, which sometimes extend into the pulp via the rima ungualum, an area delineated by the distal phalanx and Flint’s ligament (Fig. 6.34). The surgical approach is planned according to the size and location of the tumor. The lateral type may be excised by a lateral approach and lifting of the nail bed without disruption of the matrix. The median type may need a transungual approach, and the resection size will need to be adapted to the size of the tumor.

Sagittal MR images are essential to determine the relations between the tumor and the nail matrix. The lesions beneath the matrix are difficult to detect. Clinically, they
are often unsuspected, although they may lead to a nail fissure by compression of the matrix. The supporting dermis of the matrix presents specific features on MRI, as an oval area with a high signal on T2-weighted images and a high enhancement after injection of gadolinium [4]. These patterns decrease the contrast between healthy tissue and tumor on all sequences (Fig. 6.27). In addition, this oval area beneath the matrix may be particularly intense and must not be confused with a glomus tumor. Axial 3D gradient echo images and the injection of gadolinium may help to highlight a faint erosion of the cortex and a peripheral capsule.

More rarely, the lesions may be located in the pulp or the posterior nail fold. In this case, the contrast of healthy tissue/tumor is completely different because of the fat tissue of the hypodermis surrounding the tumor. The low-signal tumor is spontaneously visible on T1-weighted images, surrounded by the high signal of fat. On the other hand, the injection of gadolinium blurs the tumor limits by leveling out the signals (Fig. 6.34). T1-weighted fat-suppressed sequences with the injection of gadolinium yield the best contrast between the low signal of the fat and the enhanced tumor.
Vascular malformations of the fingertip are mainly venous malformations or capillary malformations. Arteriovenous malformations, hemangiomas, epithelioid hemangioendothelioma, and false aneurysms are very rare in adults. Hemangiomas are located in the superficial dermis limited to the epithelial layer.

Radiographs can depict a mass in the soft tissues, phleboliths, and even bone erosion (Fig. 6.35). The bone may be primarily involved by vascular malformation (linear striations parallel to the shaft of the phalanx) or an aneurysmal bone cyst (expansive osteolytic lesion of the phalanx).

Both imaging modalities easily show the vascular patterns of the malformation, but are not able to differentiate between each vascular type. Phleboliths present hyperechoic foci with posterior acoustic shadowing. Doppler ultrasound and MRI can assess the architecture and extension of the vascular malformation. Doppler US shows abnormal low-resistance arterial...
signal with forward flow during systole and diastole \[32\]. Blood flow velocity waveforms with Doppler ultrasound or dynamic enhanced MR images allow separation of low-flow from high-flow vascular lesions (Fig. 6.36). Flow void artifacts or an early enhancement with a delayed washout on MRI favor a high-velocity malformation (Fig. 6.37). Cystic blood-filled spaces with horizontal fluid–fluid levels may be encountered in low-flow lesions. Imaging also assesses the extension of the lesion in the soft tissues and the relations with the proper digital vessels. The original location, soft tissue or bone, is well depicted on MR images \[33\]. CT angiography and MR angiography with 3D MIP reformatted images are the best imaging modalities to assess the architecture and the nidus of the vascular malformation with serpentine or lattice-like patterns.

**Pyogenic granuloma**

The term “lobular capillary hemangioma” should be used and reflects a presumed neoplastic process rather than the usually suggested trauma or infection etiologies. Diagnosis is evoked with a bright red colored and rapidly growing cutaneous mass of the fingertip. Ulceration and bleeding are common but 18% of lesions may be misdiagnosed. US demonstrates a well-defined mildly to moderately echogenic mass with small hypoechoic foci.

Figure 6.35  Cavemous hemangioma. Lateral radiograph with a volar mass in the soft tissues and a bone erosion of the distal phalanx.

Figure 6.36  Low-flow malformation of the lateral nail fold. High signal of the malformation (arrow) on axial short time inversion recovery (STIR) (a) and fat saturation postenhanced T1-weighted (b) images. Magnetic resonance angiography: early enhancement (c) with increased uptake and extension on the delayed phase (d).
The high vascularization of the mass with an arterial waveform of the internal blood flow is depicted with Doppler US [34]. Therefore, US can differentiate the more echogenic lobular capillary granuloma from other subungual vascular malformations (glomus tumors and other vascular malformations). MR findings are non-specific with a low signal on T1-weighted images, high signal on T2-weighted images, and a strong enhancement after injection of gadolinium (Fig. 6.38) [35].

Neuromas

Neuromas develop from the numerous nerve fibers in the nail bed and in the pulp after an injury or repeated microtraumas. US and MRI can detect a well-circumscribed nodule in the nail bed or the pulp, along the terminal course of a proper digital nerve. The signal of the lesion is low to intermediate on T1- and T2-weighted images. Usually there is no or only a faint enhancement after injection of gadolinium (Fig. 6.39). This enhancement is increased by fat suppression.

Schwannomas and neurofibromas

These rarely occur in the subungual area. The lesions present sharp limits and show a strong enhancement of the whole or a part of the tumor on MR images. A cystic component is possible. The signal is very high on T2-weighted images (Fig. 6.40). In schwannomas of the proper digital nerve, US and MRI can demonstrate the eccentric position of the tumor beside the nerve.

Giant cell tumors

At the level of the fingers, the tumor is most often solitary and developed from the tendon sheath of either the flexor digitorum profundus tendon or the extensor tendon. More rarely, the lesion originates from the distal interphalangeal joint and is a true pigmented villonodular synovitis. Radiographs show the thickening of the soft tissues and sometimes associated bone erosion of the cortex of the phalanx [36]. These tumors rarely involve the nail apparatus. There are no calcifications, in contrast to synovial sarcomas. US may be helpful in identifying solid masses with a high vascular component on Doppler images (Fig. 6.41). Despite the lack of a specific pattern, the diagnosis may be suggested by the presence of the lesion in the vicinity of a tendon sheath and the high frequency of this pathology. The tumor usually extends eccentrically from the tendon sheath. A low-signal component of the tumor on T2-weighted imaging is evocative and a gradient echo sequence must be
added to highlight the hemosiderin deposits with specific magnetic susceptibility artifacts (Fig. 6.42). On the other hand, the signal enhancement after the injection of gadolinium is not specific.

**Lipomas**

Lipomas may be tricky with ultrasound whereas they are easily recognized on CT or MR images with specific patterns (negative densities with CT and high signal on T1-weighted images). The signal is canceled with a fat suppression before saturation.
Osteocartilaginous tumors

Exostoses and osteochondromas
Benign tumors are by far the most frequent and mainly include subungual exostoses and osteochondromas. The distinction between these two lesions is vague and debated and most cases are an osteochondromatous proliferation secondary to repeated microtrauma in exposed areas, particularly at the great toe tip. The diagnosis is easy on radiographs with a well-defined pedunculated or sessile bone growth at the dorsal or dorsomedial aspect of the cortex of the distal phalanx (Fig. 6.43). US demonstrates a well-defined hyperechoic lesion with posterior acoustic shadowing. A cartilaginous cap, usually thinner than 2 mm, appears hypoechoic. Doppler imaging may show peripheral inflammation or infection of the nail bed [37]. Most often, MRI is not necessary for the diagnosis but can easily depict a cartilaginous cap. Proton density-weighted or 3D gradient echo images are the most accurate and can distinguish hyaline cartilage with high signal (Fig. 6.44) from fibrocartilage with lower signal (Fig. 6.45). These two components may be associated and the thickness of the cap can be accurately measured. The trabecular bone is nicely visible on gradient echo images, where the trabecular network is increased by the magnetic susceptibility artifacts. In our experience, MRI demonstrates in most cases cortical and marrow continuity, but this is debated. However, MRI is mainly indicated to highlight a purely radiolucent cartilaginous exostosis (Fig. 6.46).

Chondromas
Enchondromas are the most frequent bone tumors of the hand and account for almost 50% of all cases. Radiographic findings of enchondromas are specific with lobulated radiolucent defects, bone expansion, and flecks of calcification (Fig. 6.47). Periosteal chondromas (4.6% of all chondromas) appear as well-circumscribed intracortical radiolucencies and radiograph findings may be subtle. They are more common in enchondromatosis (Ollier disease) (Fig. 6.48). High-resolution MRI more accurately depicts these abnormalities on axial gradient echo images and also reveals the cartilaginous signal of the tumor with a low signal on T1-weighted images and a high signal on T2-weighted images, identical to that of water, and a faint peripheral enhancement without visible septa (Fig. 6.47). Usually, this cartilaginous component is less important in the parosteal osteochondromatous proliferations [38].

Chondromas may be purely located in the soft tissues with small nodules of cartilage without any connection to the underlying bone [39]. Soft tissue chondromas involve mainly the fingers in patients between 30 and 60 years old. Radiographs show an enlarged nail bed.

Figure 6.43 Subungual exostosis. Posteroanterior radiograph.

Figure 6.44 Subungual exostosis with a high-signal hyaline cartilage cap (arrows). Axial gradient echo image.

Figure 6.45 Subungual exostosis with a 1-mm-thick fibrocartilage cap (arrows). Axial gradient echo image. Note the central core of trabecular bone.
without abnormalities of the underlying phalanx and foci of calcifications in 33–70% of cases [40, 41]. US depicts a well-defined hypoechoic mass in the nail bed with variable vascularization on Doppler imaging. MRI is more specific with a lobulated architecture of the mass and high signal on T2-weighted images of the hyaline cartilage. Septa and the periphery of the mass enhance after injection of gadolinium (Fig. 6.49). Calcifications present a low signal on all sequences [42].

Osteoid osteomas
Osteoid osteomas are rare at the level of the distal phalanx. About 8% of osteoid osteomas involve the phalanges. Lesions of the distal phalanx rarely present the typical nidus on radiographs (Fig. 6.50) but rather non-specific osteosclerosis or periostitis (Figs 6.51, 6.52). CT with thin contiguous slices is the best imaging technique to detect the nidus in a subperiosteal, cortical, or intramedullary location, especially guided by previous ⁹⁹mTc scintigraphy (Figs 6.50, 6.53). However, even on CT slices the lesion may be difficult to locate accurately. High-resolution MRI may be helpful to confirm the diagnosis (Figs 6.52, 6.53). MR angiography of the fingertip with MIP reformatting better shows the highly vascular nidus (Fig. 6.54). MRI is the best technique to depict the associated abnormalities: a large inflammatory reaction of the nail bed and bone edema of the distal phalanx (Fig. 6.51). A synovitis of the distal interphalangeal joint may be associated.

Giant cell tumors of bone
The distal phalanx of young adults may present a giant cell tumor. However, metacarpal bones are more commonly involved. Radiographs show a purely lytic expanding
lesion of the cortex and cancellous bone. The typical eccentric metaphyseal location may be difficult to depict on the distal phalanx. CT scan better shows the lack of calcifying matrix. The tumor signal is variable on MR images with a specific low-signal component due to fibrosis and hemorrhage (Fig. 6.55). Fluid–fluid levels may reveal an aneurysmal transformation.

Multiple giant cell bone tumors are rare and a hyperparathyroidism must be evoked. Acroosteolysis and subperiosteal resorption may be depicted on hand radiographs. Bone scan provides whole-body imaging of the multiple bony lesions.

Figure 6.47 Enchondroma of the distal phalanx. (a) Posteroanterior radiograph: bone expansion and cortex rupture. (b) Axial T2-weighted spin echo image: high signal of hyaline cartilage (*) and endosteal scalloping of cartilage lobules. (c) Sagittal postenhanced T1-weighted spin echo image: lack of enhancement of cartilage and enhancement of periphery and septa (white arrows). Displacement of the nail root (black arrows).

Figure 6.48 Ollier disease. Multiple exenterate chondromas (arrows) involving all phalanges.
Diagnosis of subungual malignant tumors may be delayed because clinical findings are sometimes minimal and non-specific and may be confused with benign lesions. US and MRI are not routinely indicated in these conditions and must not delay a biopsy. US accurately depicts a hypoechoic subungual mass with internal or peripheral neovascularization on Doppler images, but findings are non-specific. MRI is also poorly specific but provides a better extension of the tumor, particularly at the distal phalanx.

**Squamous cell carcinoma**

Subungual location is rare but squamous cell carcinoma is one of the most common primary malignant tumors of the nail bed. This low-grade malignant lesion may be confused with a viral wart, a benign dermatosis, or a fungal infection. The diagnosis may also be obscured by a secondary infection.

MRI findings are non-specific with low signal on T1-weighted images, intermediate signal on T2-weighted images, and a heterogeneous enhancement. A simple reactional bone edema or a secondary infection is possible but a true bone invasion should be discussed. The sharp limits of a very low signal of bone on T1-weighted images favor tumoral invasion. Subungual typical fibroxanthoma, a rare mesenchymal skin tumor of intermediate malignancy, presents similar patterns on MRI [43].

**Malignant melanoma**

Subungual melanoma is uncommon and affects mainly the thumb and the great toe. In this location the melanoma is easily amelanotic. Specific signal patterns of melanin (high signal on T1-weighted images and low signal on T2-weighted images) are rarely encountered on MRI. The low amount of melanin or the high frequency of amelanotic types may be responsible. Intratumoral hemorrhage is usually the cause of paramagnetic effects (Fig. 6.56).

**Chondrosarcoma**

If the occurrence of pain is rare with enchondromas, except in cases of pathological fracture, conversely it is common with chondrosarcoma. The diagnosis of malignancy may be difficult on a distal phalanx where enchondromas may present bone expansion and cortex fracture. However, focal areas of ill-defined osteolysis and extensive destruction of the cortex with calcifications in the soft tissues are suspicious (Fig. 6.55). MRI is helpful and shows abnormal patterns for a simple enchondroma. The extension to the nail bed may be large with lifting of the nail plate. Some areas show typical signal behavior of
Figure 6.51 Osteoid osteoma of the distal phalanx. (a) Lateral radiograph: osteosclerosis and diffuse periosteal reaction of the distal phalanx. No visible bone nidus. (b) Bone scan: spotty uptake of the distal phalanx. (c) Sagittal T1-weighted spin echo images before (below) and after (above) injection of gadolinium: low signal of a diffuse bone edema (below) and strong enhancement of the periosteal reaction and the inflammatory nail bed. Secondary sagittal hypercurvature of the nail plate.

Figure 6.52 Osteoid osteoma of the distal phalanx. Non-specific osteosclerosis or periostitis.

Figure 6.53 Osteoid osteoma of the distal phalanx. Sagittal postenhanced gradient echo image. A round distal nidus of the tuft presents a high signal.
hyaline cartilage, but other areas present an unusual mottled enhancement (Fig. 6.57).

**Conclusion**

Despite the high value of clinical examination of the nail apparatus, radiographs remain necessary if a deep mass is suspected beneath the nail plate. High-frequency US may be helpful in experienced hands, but high-resolution MRI offers the most promising developments for imaging of the nail apparatus.

Figure 6.54 Osteoid osteoma of the distal phalanx. (a) Sagittal T2-weighted spin echo image: calcifying low-signal nidus (*) with bone edema of the whole distal phalanx and inflammatory reaction of the nail bed. (b) Magnetic resonance angiography, arterial phase: early enhancement of the nidus (arrow).

Figure 6.55 Giant cell bone tumor of the distal phalanx. (a) Posteroanterior radiograph: osteolysis of the tuft with a peripheral bone sclerosis and a distal cortex rupture (arrow). (b) Axial T1-weighted magnetic resonance image before (above) and after (below) injection of gadolinium: strong enhancement of the whole tumor. The extension to the nail bed (*) is better depicted after injection.
References


Chapter 7

Nail Fold Capillary Microscopy or Capillaroscopy

Gregor B.E. Jemec

Department of Dermatology, Zealand University Hospital, Roskilde; Health Sciences Faculty, University of Copenhagen, Copenhagen, Denmark

Introduction

The in vivo assessment of the microvasculature is best known from ophthalmology, in which changes in the vessels of the eye can be viewed and classified to provide important diagnoses such as hypertension. Similarly, imaging of the skin microvasculature can be done on the proximal nail fold, where it is traditionally used in the diagnosis of autoimmune disease. Autoimmune disease affects the morphology of the vessels that can, therefore, be identified and classified by nail fold capillary microscopy or capillaroscopy [1]. The overlap between dermatology and rheumatology in the management of autoimmune disease such as lupus erythematosus or scleroderma makes a short overview of qualitative capillaroscopy relevant for dermatologists.

Technology

Capillaroscopy can be carried out with a variety of tools ranging from simple dermoscopes with low magnification to dedicated videocapillaroscopes and Doppler optical coherence tomography. Figure 7.1 shows an image obtained through an ordinary dermoscope and enlarged electronically. Although dedicated tools such as videocapillaroscopes offer the possibility of detailed imaging and a semiquantitative approach, the method has utility in a wide range of devices and magnifications, suggesting that ordinary dermoscopes may be of help in a routine clinical setting.

The use of a suitable coupling medium is necessary, e.g. a mineral oil. There is no consensus on how many fingers should be examined (range 1–10), but for simple screening it is not difficult to examine the four lateral fingers on each hand. No fixed rules exist, however, and as the presence of the microvascular changes is driven by systemic disease it has been suggested that the sampling may be restricted to the middle finger of the dominant hand without significant loss of diagnostic accuracy [2]. Users may inadvertently compress the microvasculature on application of an imaging device to the proximal nail fold, and thereby influence the quality of the imaging. It is recommended to routinely test the ability of any chosen method on normal tissue first.

Normal nail fold microvasculature

The terminal vascular unit contains terminal arterioles, initial veins, junctional canals, and capillaries and is the focus of capillaroscopy. The capillaries consist of a single layer of endothelial cells surrounded by a double basal layer with pericytes and contained in a matrix of loose connective tissue. Terminal vascular units in the skin are usually perpendicular to the surface (vertical); therefore capillaries are generally seen only as pinpoints. The nail fold forms an important exception to this
because of its horizontal growth, which allows a ‘sideways’ view of the vessels.

Like other imaging techniques capillaroscopy is based on pattern recognition and therefore is subject to inter- and intraobserver variation. Normal nail fold anatomy is, however, usually literally at hand (the reader’s) for reference, which may aid in the identification of abnormal microvascular patterns.

Normal capillaries appear in a regular, even distribution and do not involve the cuticle. The distribution has been described as that of a comb facing the nail. On closer inspection each vessel is thin with an even diameter and a hairpin shape, which is usually open but may appear “crossed” or “twisted” at the very end. It has been suggested that only the open lops are normal, while the “crossed” capillaries are non-specific changes (Fig. 7.2) [3]. A few abnormal shapes and ectatic vessels may, however, be found in healthy individuals as they can be reactive to, for example, local trauma, but they neither predominate nor persist.

Capillary pathology

Capillary pathology is associated primarily with differentiating primary from secondary Raynaud phenomenon, systemic scleroderma, and dermatomyositis. The following features are identified.

- Hemorrhages. These are often seen even at low magnification. In addition to the morphology of the capillaries the surrounding tissue should also be examined. Vascular damage due to either progressive vasculitis or trauma leads to extravasation of blood, which may be easily seen. Usually the appearance of a “necklace” pattern is associated with angiopathy, whereas blotches are associated with trauma.
- Areas where the capillaries have disappeared (lower density than 9–13 capillaries/mm of proximal nail fold). This requires sufficient magnification for the visualization of individual capillaries (usually a
minimum of × 50 magnification), and therefore is not as widely available outside specialized clinics.

- Giant capillaries (ectatic vessels). This is seen either as a part of general vasodilatation (transient) or as a specific consequence of microangiopathy in scleroderma, dermatomyositis, lupus erythematosus, or sclerodactylyia due to, for example, vinyl chloride poisoning.

- Abnormally shaped capillaries (neovascularization). Capillaries of the proximal nail fold are usually very regular, and irregularities such as elongated loops, asymmetry between afferent and efferent capillaries, microaneurysms, or tortuous or ramified loops are generally associated with autoimmune diseases such as lupus erythematosus and rheumatoid arthritis (Fig. 7.3).

Capillaroscopy is a clinical sign and is not pathognomonic. The presence of microvascular abnormalities should therefore lead to a general assessment of the patient and further diagnostic tests directed by the patient’s history and other clinical findings. Abnormal capillaroscopy may also be seen as a result of, for example, diabetes, hypertension, or occupational factors such as vibration.

References


Chapter 8

Confocal Microscopy

Sébastien Debarbieux¹, Amélie Boespflug¹, Bruno Labeille², and Luc Thomas¹

¹ Department of Dermatology, Centre Hospitalier Lyon Sud; Lyon Cancer Research Center (Pr Puisieux); Lyon 1 Claude Bernard University, Lyon, France
² Dermatology Department, Hôpital Nord, Saint Etienne, France

Introduction

Since the previous edition of this book many more reports on the use of confocal reflectance or fluorescence microscopy have been published, leading to this new chapter. Reflectance confocal microscopy is a mainly in vivo technique, and is available in only a few centers worldwide. It offers a new way of imaging cutaneous lesions at a quasi-histopathological level, but its main limitation is the very narrow range of penetration through the skin surface. This limitation is the main reason for its only relatively recent development in nail diseases. Ex vivo confocal microscopy can be performed in both reflectance and fluorescence modes and offers an alternative to frozen sections in the extemporaneous examination of a skin biopsy specimen with the main advantage that the technique does not damage the specimen, which may afterwards undergo classical histopathological paraffin-embedded sectioning and staining without any loss of pathological material.

These two techniques appear, in our view, to be of particular interest in nail tumors because of the small size of the lesions (ex vivo) and because of the possibility, through extemporaneous diagnosis of malignancy in preoperatively doubtful cases, to offer a one-step treatment of the diagnosed condition, thus reducing waiting times for patients (in vivo and ex vivo).

Equipment and technical aspects

Although expensive and time consuming, dermatology-dedicated in vivo reflectance confocal microscopes and ex vivo reflectance and fluorescence confocal microscopes are nowadays available in an increasing number of large university hospital dermatology referral centers in Europe and, to a lesser extent, worldwide.

In vivo confocal microscopy

In vivo confocal microscopy digitally detects the light reflected by skin microstructures illuminated by a laser beam transmitted through the same optical device as used for detection (con-focal method). Highly reflective material, mainly melanin, included in the tissue will appear white, whereas non-reflective material, mainly water, will appear black.

The image is constructed by point-by-point sequential scanning of black, white, and different shades of gray (corresponding to the different reflectivity characteristics of the illuminated material). Very precise
focusing of the detected reflectance produces virtual horizontal sectioning of the tissue being examined with micrometer definition; however, there is a limited vertical depth of investigation of about 200 μm on the skin. Two operating systems are available. (i) The large-field detector provides images of lesions similar to those obtained with dermoscopy and allows examination of a larger field; however, this detector requires a positioning ring that is much too large to be applied to any part of the nail unit. (ii) The handheld detector produces similar images but with a narrower field of examination, and since the surface area in contact with the tissue is much smaller it is perfectly adapted to the nail anatomy; moreover, it does not need to be positioned by an external device. In vivo confocal microscopy produces live images that can be stored for subsequent examination. Indeed, just like the larger field system, micrometric virtual horizontal sectioning is possible, thus producing images at different depths from the surface to the deepest available examination level.

As this examination level is very narrow, it is not possible to visualize structures through the nail plate. This was the main limitation of the technique in the diagnosis of onychomycoses [1] until the publication by Debarbieux et al. [2], who first described the peroperative examination of subungual structures after nail plate avulsion.

In vivo reflectance confocal microscopy of the nail is mainly used in the differential diagnosis of melanocytic tumors during surgical procedures on the nail bed and in matrix exploration. In order to visualize the entire surface of the matrix from the distal part of the lunula to the proximal matrical cul-de-sac, it requires, after nail plate avulsion under local anesthesia (trapdoor technique, lateral avulsion, or complete nail plate avulsion), sterile isolation of the surgical field with a translucent sterile wrap. Direct examination of the subungual structures by the handheld detector is possible though sterile oil immersion of the optical lens. Images can be obtained from different examination depths during live examination of the structures, although evaluation of the dermoepithelial junction is of particular interest in early subungual melanomas. The main advantage of this technique is to offer in the majority of preoperatively doubtful cases of melanonychia striata an extemporaneous diagnosis of malignancy. This allows wide excision of the nail unit to be offered within a single surgical session, thus reducing dramatically the waiting times for patients when compared with the biopsy-then-excite two-step classical melanoma management procedure [2–4].

**Ex vivo confocal microscopy**

Not all skin tumors contain enough reflective material to allow a diagnosis by reflectance confocal microscopy. Moreover, the abundance of hyperkeratotic material overlying the keratinizing tumors is too thick for in vivo reflectance confocal microscopy. In this case exogenous fluorescent dyes can be used to enhance the contrast and to allow better visualization of the microstructures. This is the purpose of fluorescence confocal microscopy. Unfortunately, there is currently no sufficiently safe transpidermally bioavailable fluorescent dye available; therefore, this technique can only be used ex vivo. Ex vivo confocal microscopes are bimodal and offer reflectance mode imaging as well as fluorescence mode imaging at different wavelengths. The use of acridine orange, which stains the nuclei of cells, allows the production of good quality micrometer-scale histopathological images. However, in contrast with reflectance microscopy, no virtual sectioning is possible since acridine orange only dyes the surface of the tissue specimen in contact with the dye.

The freshly excised tumor is bisected into two parts and then placed into the dye. After rinsing the dye off the specimen, the two bisected parts of the tumor are placed, sectioned side up, on a glass slide that is directly mounted facing toward the optical lens of the device. An image (up to 2 × 2 cm) is obtained by point-by-point scanning of the surface of the specimen. A completely unique image is obtained within 5–15 min depending on the size of the examination field. The device offers the possibility to precisely retarget specific areas of the lesion for further high-power examination. The main advantage of this technique is to offer a good alternative to classical frozen section extemporaneous examination of tumors with complete conservation of all surgically excised tissue (albeit bisected into two parts); this allows further classical paraffin-embedded tissue processing for pathological examination. In our view this is a particular advantage in nail tumors, which are usually too small to allow for any loss of pathological material [5].

**Areas of interest**

Confocal microscopy in nail disease is rapidly developing, so we will focus only on peer-reviewed published material [6, 7].

**Fungal infections**

The first use of confocal microscopy ever published was for the diagnosis of a fungal infection [1]. More recently, Pharaon et al. [8], taking advantage of a deeper field of examination within the nail plate compared with the skin (400–500 μm), which was insufficient to examine the subungual structures, clearly demonstrated the ability of reflectance confocal microscopy...
to monitor onychomycosis during antifungal therapy on a large series of 58 patients (Fig. 8.1).

Melanocytic nail tumors

The differential diagnosis of melanonychia striata is sometimes extremely difficult (see Chapters 4 and 21). Melanoma should always be considered, yet doubtful cases remain after thorough clinical dermoscopic and even peroperative dermoscopic examination. In many cases only a histopathological examination of a nail matrix biopsy specimen will provide the final diagnosis. However, after confirmation of a histopathological diagnosis of melanoma, treatment, i.e. wide excision of the nail unit, still needs to be carried out. When including any time required for the histopathological diagnosis and delays in obtaining a surgical appointment, the time that a patient is waiting with an injured toe or finger increases to weeks or months. This is why we believe that there is a place for in vivo reflectance confocal microscopy to provide a preliminary report and then a more thorough study during the surgical exploration of the nail matrix in cases of suspected or doubtful melanonychia striata [2, 3]; when confirmed during the surgical procedure, wide excision of a melanoma can be performed immediately (Fig. 8.2). In the case of a confocally benign-looking lesion a less aggressive shave biopsy of the nail matrix can be offered to better preserve the subsequent regrowth of the nail plate if the diagnosis of a benign condition is confirmed by the pathologist (see Fig. 4.49). Interestingly several cases of pigmented Bowen disease/squamous cell carcinoma of the nail unit have also been peroperatively diagnosed in our center [3, 4].

Other tumors

In vivo reflectance confocal microscopy is of little help in unpigmented tumors because of the low reflectance of their microscopic content and because of the thickness of their hyperkeratotic superficial component. However, Sanchez et al. [9] have demonstrated the microtubular architecture of onychomatricoma in one case. The differential diagnosis of unpigmented nail unit tumors is sometimes difficult, and this is particularly the case for onychomatricoma, squamous cell carcinoma (Fig. 8.3), viral warts, keratoacanthoma, callus and, to a lesser extent, onychopapilloma. Again the classical “biopsy-then-treat” management scheme results in a long waiting time for the patient. Classical frozen section histopathological extemporaneous examination cannot be offered for very small subungual tumors because of the potential loss of tissue to be subsequently submitted to pathology. Ex vivo reflectance confocal microscopy overcomes these two difficulties by enhancement of the contrast by application of a fluorescent dye that will allow visualization of the microscopic architecture of the lesion without damage to the specimen before it undergoes classical histopathological tissue processing. In our experience this allows extemporaneous diagnosis of onychomatricoma (Fig. 8.3), squamous cell carcinoma (Fig. 8.4), glomus cell tumor (Fig. 8.5), and neuroma (Fig. 8.6), and, probably, many other diseases can be diagnosed [5].
Figure 8.2 (a) Acral lentiginous melanoma of the nail matrix, Clark’s level II and Breslow’s thickness 0.35 mm. Dermoscopy (b) as well as surgical inspection (c) and peroperative dermoscopy (d) showed suspicious features. In vivo reflectance confocal microscopy (e–g) shows numerous enlarged highly reflective atypical cells at the dermal–epidermal junction and in the dermis with an irregular disposition of the cells and nests, confirming at an almost histopathological level the diagnosis of melanoma. This allowed a one-step surgical procedure of wide excision of the nail unit and graft (h) and a shorter postoperative recovery time. The patient was able to walk normally and wear regular shoes less than 1 month after the procedure (i).
Figure 8.3 (a) Onychomatricoma. Dermoscopy (b), dermoscopy of the free edge (c), surgical inspection (d), and peroperative dermoscopy (e) showed indicative features of onychomatricoma but did not confirm the diagnosis. Extemporaneous ex vivo fluorescence confocal microscopy of the freshly excised tumor after longitudinal bisection and incubation in acridine orange solution (h–l) showed the typical epithelial–connective tissue architecture of onychomatricoma, which correlated perfectly with the subsequent histopathological examination (f,g) of the same unaltered specimen, allowing conservative treatment of the tumor.
Figure 8.4 (a) Squamous cell carcinoma of the nail bed. Dermoscopy (b), surgical inspection (c), and peroperative dermoscopy (d) showed a subungual keratinizing tumor but malignancy could not be determined. Extemporaneous ex vivo fluorescence confocal microscopy of the freshly excised tumor, bisected longitudinally and examined after incubation in acridine orange, shows typical dermal round-shaped proliferating nodules (e–g) that correlated perfectly with the microanatomy of the lesion (h,i).
Figure 8.5  (a) Subungual glomus cell tumor of the nail bed. The lesion was almost invisible clinically. Dermoscopy (b,c) indicated a non-specific red spot in the nail bed region. Extemporaneous ex vivo fluorescence confocal microscopy (d) of the freshly enucleated tumor after bisection and incubation in acridine orange solution showed the typical cytology and architecture of this tumor with perfect pathological correlation (e,f).

Figure 8.6  (a) Subungual neuroma. (b) Extemporaneous ex vivo fluorescence confocal microscopy of the bisected freshly excised tumor after incubation in acridine orange showed the typical architecture and cytology of this tumor.
References


Part III

Nail Disorders Occurring Principally in Childhood

Chapter 9

Hereditary and Congenital Nail Disorders

Smail Hadj-Rabia, Rudolf Happle, Bianca Maria Piraccini, and Robert Baran

Table 9.1. Syndromic congenital nail disorders are reported in

<table>
<thead>
<tr>
<th>NAIL REGION</th>
<th>264</th>
</tr>
</thead>
<tbody>
<tr>
<td>Secondary nail changes and some miscellaneous nail conditions, 254</td>
<td></td>
</tr>
<tr>
<td>Tuberous sclerosis complex, 255</td>
<td></td>
</tr>
</tbody>
</table>

MOSAIC DISORDERS INVOLVING THE NAIL REGION, 264

Introduction, 264

Hamartomas, 264

Periungual fibromas of tuberous sclerosis, 264

Acral keratotic lesions of PTEN hamartoma syndrome, 264

Storiform collagenoma, 264

Nevus sebaceus, 264

Neurofibroma, 264

Glomus tumor, 265

Glomus tumors as a feature of neurofibromatosis 1, 265

Melanocytic nevus, 265

Onychomatricoma, 265

Eccrine angiomatous hamartoma, 265

Nail disorders reflecting functional X-chromosome mosaicism, 265

CHILD nevus, 265

Conradi–Hünermann–Happle syndrome, 267

Incontinentia pigmenti, 267

Focal dermal hypoplasia, 267

Börjeson–Forssman–Lehmann syndrome, 267

Other mosaic disorders involving the nail region, 268

Inflammatory linear verrucous epidermal nevus (ILVEN), 268

Linear psoriasis, 268

Lichen striatus, 268

Superimposed linear lichen nitidus, 268

Happle–Tinschert syndrome, 268

Porokeratotic eccrine nevus, 269

Linear porokeratosis groove, 269

Linear Darier disease, 270

CONGENITAL AND HEREDITARY DISORDERS INVOLVING THE NAILS, 213

Introduction, 213

Nail embryology, 214

Anonychia, 215

Anonychia with other symptoms, 216

Nail–patella syndrome or hereditary osteoonychopalasia, 216

Ectodermal dysplasias, 227

Hypohidrotic ectodermal dysplasia, 227

Pachyonychia congenita, 227

Dyskeratosis congenita, 238

Trichothiodystrophy, 239

Disease loci and chromosome anomalies, 240

Nail change in syndromes with predominantly skeletal anomalies, 240

Hypoplastic or atrophic nails with skeletal anomalies, 241

Hyperonychia, hyperplastic thick nails, onychogryphosis, 241

Clubbing, acropathy, Hippocratic nails, 245

Broad nails and pseudoclubbing, 246

Isolated congenital nail dysplasia, 247

Koilonychia (spoon nails), 248

Curved nail of the fourth toe, 248

Overcurvature of the nails, 248

Ectopic nails, onychoheterotopia, 248

Congenital malformations caused by drugs or infections, 250

Nail discoloration, 250

Epidermolysis bullosa, 250

Secondary nail changes and some miscellaneous nail conditions, 254

Nail Disorders Occurring Principally in Childhood

Chapter 9

Hereditary and Congenital Nail Disorders

Smail Hadj-Rabia, Rudolf Happle, Bianca Maria Piraccini, and Robert Baran

Introduction

Many defects of the nails are accompanied by developmental changes in other organs, such as skin, teeth, brain, and bones. The many abnormalities of the nails described here are often of minor importance when making a diagnosis. Of greater interest are apparently isolated nail defects, since they may help in the diagnosis of hidden syndromes or more generalized disease. In categorizing these disorders the nail is the main focus, but disorders have also been grouped according to the most obvious symptoms. The goal of such a practical division is to aid the physician observing nail changes in establishing the diagnosis. Non-syndromic congenital nail disorders are reported in Table 9.1.
In view of the large number of unique and rare syndromes associated with nail involvement, the majority of this chapter is best understood through the associated comprehensive tables stressing the nail apparatus changes and major associated abnormalities. The MIM (Mendelian Inheritance in Man) numbers have been added when available [1]. Autosomal entries initiated before 20 May 1994 have numbers between 100050–195002 and 200100–280000. Later appearing autosomal entries are numbered 600000–601922. X-linked disorders are numbers 300000–315000, Y-linked 400000–490000, and mitochondrial entries are numbers 502000–598500. An asterisk indicates that an entry describes a distinct gene or phenotype. Absence of the sign preceding the number indicates that the distinctness of the phenotype or the characterization of the gene in the human as not established. The # sign signifies that the phenotype is caused by a mutation in a gene also represented by other entries.

Table 9.1 Non-syndromic congenital nail disorders.

<table>
<thead>
<tr>
<th>Type, MIM number</th>
<th>Nail symptoms</th>
<th>Mode of inheritance, gene, mapping</th>
<th>Other manifestations</th>
</tr>
</thead>
<tbody>
<tr>
<td>NDNC-1, MIM161050</td>
<td>Trachyonychia</td>
<td>AD</td>
<td>Nails are variably involved. Thinning, thickening, pitting, opalescence, absence of thumb nails, longitudinal ridges, discoloration are possible. Koilonychia is sometimes reported</td>
</tr>
<tr>
<td>NDNC-2</td>
<td>Koilonychia</td>
<td>AD</td>
<td>True, apparent or pseudoleukonychia belong to this group</td>
</tr>
<tr>
<td>NDNC-3, MIM151600</td>
<td>Leukonychia</td>
<td>AR and AD, PLCD1, 3p21.3</td>
<td>Possible remnants or rudimentary nail plates</td>
</tr>
<tr>
<td>NDNC-4, MIM206800</td>
<td>Anonychia, hyponychia congenita</td>
<td>AR, RSPO4</td>
<td>Increased transverse curvature and absent lunulae are possible</td>
</tr>
<tr>
<td>NDNC-5, MIM164800</td>
<td>Distal onycholysis</td>
<td>AD</td>
<td>Thumbs and great toe are more severely affected. Anonychia is reported.</td>
</tr>
<tr>
<td>NDNC-6, MIM107000</td>
<td>Partial absence of nails</td>
<td>AD</td>
<td>Thinning of nail plate, poorly developed or absent lunulae, vulnerability of the free nail margins</td>
</tr>
<tr>
<td>NDNC-7, MIM605779</td>
<td>Longitudinal streaks</td>
<td>AD, 17p13</td>
<td>“Two compound heterozygous families</td>
</tr>
<tr>
<td>NDNC-8, MIM607523</td>
<td>Isolated toenail dystrophy</td>
<td>AD, (3p21.3, COL7A1)*</td>
<td></td>
</tr>
<tr>
<td>NDNC-9, MIM614149</td>
<td>Anonychia of toenails and onycholysis of fingernails</td>
<td>AR, 17q25</td>
<td>Normal fingers and toes at birth. At 7–8 years old onychodystrophy started on finger and toenails at the same time.</td>
</tr>
<tr>
<td>NDNC-10, MIM614157</td>
<td>Nail dysplasia</td>
<td>AR, 8q22.3, FZD6</td>
<td>Started at birth, slow rate of nail growth. At 10 years old claw-like structure is reported.</td>
</tr>
<tr>
<td>ICNC, MIM119900</td>
<td>Isolated congenital nail clubbing</td>
<td>AR, 4q32-q34, HPGD, AR, 3q22, SLCO2A1, [255]</td>
<td>Bilateral, symmetric, congenital, all nails affected</td>
</tr>
</tbody>
</table>

AD, autosomal dominant; AR, autosomal recessive.
Modified from Khan et al. [254].

Nail embryology

The human nail apparatus begins to develop during the 9th week of intrauterine life; nail plate growth is evident by 14 weeks and may be complete by 20 weeks (see Chapter 1). Nail defects occurring during this period are called embryopathies, and those appearing later are the fetopathies. The embryopathies are often hereditary whereas the fetopathies as a rule are caused by vascular or mechanical factors. Some hereditary defects do not become apparent until later in life, mainly because they are due to increased susceptibility to infections or secondary damage [2]. Congenital and hereditary nail dystrophies are classified according to whether the defects occur in the nail matrix, the nail field, or the nail bed. A defect in the nail matrix is the most common cause of abnormal nails. The matrix can have an abnormal position, size, or quality. The nail field is the area in which the entire nail unit (nail matrix and nail bed) develops. Proliferation of the nail bed will produce a
thickened nail which, as in pachyonychia congenita, is not evident until early childhood.

Anonychia

Total absence of all nails from birth is rare [3]. Often there are rudimentary nails on some fingers or toes (MIM 107000) (Figs 9.1, 9.2); therefore, there is frequently only a quantitative difference between anonychia and hyponychia and they often occur together [4]. The first two cases of anonychia were described in 1842 by the physician to the King of Saxony, Dr F.A. Amman; Cockayne [5] reviewed some of the earlier cases.

Isolated anonychia without other symptoms can be inherited as an autosomal dominant or recessive trait (MIM *206800) [6–8]. Cockayne [5] and Strandskov [9] described families with absent thumbnails from birth (MIM 188200). If a radiograph is undertaken an underlying bone abnormality is generally found [10]. There will be no nail if the distal phalanx is lacking; when the latter is hypoplastic the nails may be absent, dystrophic, or normal. Often anonychia is combined with other symptoms [11, 12], such as broad, small hands, due to various skeletal anomalies such as loss of phalanges (MIM 106990, *106995) or isolated fingers and toes (ectrodactyly) (MIM 106900), syndactyly (Figs 9.3, 9.4), or polydactyly.

Figure 9.1 Anonychia/hyponychia.

Figure 9.2 Anonychia/hyponychia in deafness, onychoosteoedystrophy, and mental retardation (DOOR) syndrome. Courtesy of N.C. Nevin.

Figure 9.3 Syndactyly.

Figure 9.4 Syndactyly: radiographic changes in the digits of the patient in Fig. 9.3.
In the brachydactyly variant called apical dys trophy by MacArthur and McCullough [21] or banana fingers, the four ulnar digits barely project beyond the thumb and the fingers look amputated and have no nails (Fig. 9.5). Absence of nails on the ring fingers and rudimentary nails on other fingers with brachydactyly in six generations was reported by Schott [22]. Families with total anonychia and microcephaly with normal intelligence have also been described [23]. Mutations in the RSPO4 gene have been reported in autosomal recessive forms of isolated anonychia [24].

Anonychia with other symptoms

Anonychia can occur with retarded development of the teeth [25]; Freire-Maia and Pinheiro [26] described recessive total anonychia with a dominant dental anomaly and aplasia or hypoplasia of the upper lateral incisors, spaced teeth, and lack of some molars. Loss of toenails and brachydactyly with dental changes was reported by Tennstedt et al. [27]. Congenital absence of three toenails with linear skin atrophy, scarring alopecia, and scar-like lesions of the tongue was reported by Sequeiros and Sack [28]. Absence or hypoplasia of nails on thumbs and halluces can, together with gingival fibromatosis (MIM *135500), be diagnostic features for Zimmerman–Laband syndrome [29, 30]. Anonychia can be combined with deafness, onychoostedystrophy, and mental retardation (DOOR syndrome; Fig. 9.2) (Table 9.2). These patients have an inborn metabolic error with an increase of 2-oxy glutamate in plasma and urine [31]. Pfeiffer [32] reported the otoonychoperoneal syndrome with absence of nails on thumbs, index fingers, and great toes with dysplastic ears and hypoplasia of the fibula (MIM 259780).

Anonychia is described in the rare glossopalatine ankylosis syndrome in which the mouth is abnormal, the tongue being attached to the temporomandibular joint [33]. Absence of nails on thumbs and great toe due to absence of epiphyseal centers and poor modeling of the distal phalanges was reported as a possible new autosomal disorder by Lynch et al. [34]. The patients also had a bulbous nasal tip, long philtrum, kinesigenic choreathetosis, and developmental delay. A family with dominant anonychia with bizarre flexural pigmentation (MIM 106750) and hair abnormalities was reported by Verbov [35]. Anonychia has also been described in the dyscephalic–mandibulocutaneous syndrome (MIM 234100) of Hallerman–Streiff–François with bird-like facies [36, 37] and craniofrontal nasal dysplasia (see Table 9.7). Familial absence of the fifth fingernails in combination with mental retardation, coarse facies with full lips, and scalp hypoplasia (MIM 135900) were first described by Coffin and Siris [38] (Fig. 9.6). Carey and Hal [39] and Hapesleigh et al. [40] have reviewed the literature and described new cases. Hypoglycemia in the syndrome was reported by Imaizumi et al. [41] and data on cognitive development was presented by Swillen et al. [42]. This disorder belongs to the group of epidermal dysplasias that often have other abnormalities, as described in Table 9.3. In the popliteal pterygium syndrome (Klein syndrome) the nails are missing on the fifth toe (MIM *119500). The patients also have pterygium and fissures on the first toe with syndactyly [43, 44]. In congenital onychodysplasia of the index finger (COIF) or Kikuchi syndrome the nail on the index finger can be missing (see Table 9.7). Lack of thumbnails can occur in the nail–patella syndrome.

### Nail–patella syndrome or hereditary osteoonychodysplasia (MIM* 161200)

This was described by Chatelain (1820) and Little (1897) [45]. Early diagnosis of the nail–patella syndrome or hereditary osteoonychodysplasia (HOOD) can be made by examining the nails, which give clues to the possibility of other organs being involved.

The nail changes, the most constant feature, are most pronounced on the ulnar side of the thumbs and decrease towards the fifth finger (Fig. 9.7). They are often bilateral and symmetrical. The toenails are rarely affected. The nails, especially on the thumbs, might be absent or short, narrow, spoon shaped, soft, and/or fragile. The lunula can be triangular or V shaped, which is almost pathognomonic for the condition [46, 47] (Fig. 9.8).

Individuals with nail–patella syndrome also commonly have skeletal abnormalities involving the knees, elbows, and hips. The patella is aplastic or luxated in 90% of patients (Fig. 9.9). Pain in the knee or gait problems after exercise often cause the patient to seek medical attention. The changes can result in early osteoarthritis. The radius head is small, which can cause limitation in elbow motion or subluxation of the radius. Bilateral posterior iliac horns are pathognomonic (Fig. 9.10). Other bone changes can be seen, such as scapular hypoplasia, scoliosis, genu valgum, and hypoplastic lateral humerus epicondyle.
### Table 9.2  Hereditary ectodermal dysplasia (ED) with nail changes.

<table>
<thead>
<tr>
<th>Condition</th>
<th>Inheritance, gene, mapping</th>
<th>MIM no.</th>
<th>Nails</th>
<th>Hair</th>
<th>Skin changes</th>
<th>Teeth</th>
<th>Ear</th>
<th>Eye</th>
<th>Other findings</th>
</tr>
</thead>
<tbody>
<tr>
<td>Bart–Pumphrey syndrome, PPK with leukonychia and deafness [256, 257]</td>
<td>AD, GBJ2, 13q11-q12</td>
<td>149200</td>
<td>Leukonychia on thumbs and great toes. Longitudinal white spots on other nails. Frequent koilonychia.</td>
<td>Normal</td>
<td>Hyperkeratotic areas on the knuckle pads on the dorsal side of the fingers and toes.</td>
<td>Normal</td>
<td>Deafness since birth</td>
<td>–</td>
<td>Dupuytren’s contracture</td>
</tr>
<tr>
<td>Cardiomyopathy, dilated with woolly hair and PPK [261, 265]</td>
<td>AR, DSP, 6p24</td>
<td>605676</td>
<td>Fingernail clubbing, pachyonychia</td>
<td>Woolly, abundant.</td>
<td>Striate palmoplantar and fold, occasional blisters, normal sweat, follicular keratosis of elbows and knees.</td>
<td>Loose skin (neck, palms, soles, and fingers), papillomata around the mouth and nares.</td>
<td>–</td>
<td>Cardiomyopathy</td>
<td></td>
</tr>
<tr>
<td>Dermatopathia pigmentosa reticularis [271–273]</td>
<td>AD, KRT14, 17q12-q21</td>
<td>125595</td>
<td>Longitudinal ridging and lamellar splitting</td>
<td>Sparse scalp, eyebrows, axilla.</td>
<td>Reticulate hyperpigmentation since early age often on the trunk, Adermatoglyphia.</td>
<td>Normal</td>
<td>–</td>
<td>Corneal changes. Acral bullae giving contractures.</td>
<td>–</td>
</tr>
</tbody>
</table>
### Table 9.2 (Continued)

<table>
<thead>
<tr>
<th>Condition</th>
<th>Inheritance, gene, mapping</th>
<th>Nails</th>
<th>Hair</th>
<th>Skin changes</th>
<th>Teeth</th>
<th>Ear</th>
<th>Eye</th>
<th>Other findings</th>
</tr>
</thead>
<tbody>
<tr>
<td>ED, cleft lip and palate [284]</td>
<td>AR, PVRL1, 11q23.3</td>
<td>Onychodysplasia</td>
<td>Sparse and fine scalp hair. Sparse eyelashes, eyebrows, Hypotrichosis progressive, brittle hair</td>
<td>Normal sweating, PPK, syndactyly</td>
<td>Hypodontia, anodontia</td>
<td>Anteverted</td>
<td>–</td>
<td></td>
</tr>
<tr>
<td>Condition</td>
<td>Inheritance, gene, mapping</td>
<td>Nail, Hair, Skin changes</td>
<td>Teeth, Ear, Eye, Other findings</td>
<td>MIM no.</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>-----------</td>
<td>---------------------------</td>
<td>--------------------------</td>
<td>-------------------------------</td>
<td>---------</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

(Continued)
<table>
<thead>
<tr>
<th>Condition</th>
<th>Inheritance, gene, mapping</th>
<th>MIM no.</th>
<th>Nails</th>
<th>Hair</th>
<th>Skin changes</th>
<th>Teeth</th>
<th>Ear</th>
<th>Eye</th>
<th>Other findings</th>
</tr>
</thead>
<tbody>
<tr>
<td>Ectodermal dysplasia/skin fragility syndrome [306]</td>
<td>AR, PKP1, 1q32</td>
<td>604536</td>
<td>Dystrophy, severe thickened, absent</td>
<td>Sparse and short</td>
<td>Initial pink skin with blisters of soles, perioral erythema erosions. General skin fragility with scales and crusts. Later palmoplantar hyperkeratosis. Painful walking, diminished sweating, cutaneous infections</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>No cardiomyopathy, normal intelligence, small stature, walking difficulties</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>Enamel defects. Early loss, yellow discoloration</td>
<td></td>
<td></td>
<td></td>
<td>Malalignment of great toenails common</td>
</tr>
<tr>
<td>Hystris-like keratosis [309]</td>
<td>AD</td>
<td></td>
<td>Markedly thick with distal dystrophy</td>
<td></td>
<td>Localized hyperkeratosis on pressure area of soles. Spiny keratosis on trunk, arms, legs</td>
<td></td>
<td></td>
<td></td>
<td>Long fingers. Hyperextensible joints</td>
</tr>
<tr>
<td>Keratoderma palmoplantar of Thost–Unna [93, 313–315]</td>
<td>AD, KRT1, KRT9, 12q13, 17q21</td>
<td>600962</td>
<td>Thick</td>
<td>Normal</td>
<td>Hyperhidrosis of palms and soles, non-epidermolytic PPK</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Keratoderma</td>
<td>condition</td>
<td>inheritance</td>
<td>mapping</td>
<td>normal</td>
<td>abnormal</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>------------</td>
<td>-----------</td>
<td>--------------</td>
<td>---------</td>
<td>--------</td>
<td>----------</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Keratoderma palmoplantar progressiva of Meleda [316–320]</td>
<td>AR, SLURP1, 8q24.3</td>
<td>Onychogryphosis koilonychia, short subungual hyperkeratosis, proximal part of nail pink, distal pale</td>
<td>Normal or woolly hair</td>
<td>Hyperhidrosis of palms and soles. Erythema of face and sacral region. Keratosis of elbows and knees</td>
<td>Normal</td>
<td>–</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Keratoderma palmoplantar and alopecia [321–323]</td>
<td>AD, GJA1, 6q22</td>
<td>Dystrophic nail plate. Proximal parts hyperkeratotic and brittle, leukonychia totals</td>
<td>Scanty hair. Eyebrows and eyelashes absent</td>
<td>Otherwise normal</td>
<td>Normal</td>
<td>–</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Keratoderma palmoplantar with periodontitis and onychogryphosis. Haim–Munk syndrome [329, 331, 332]</td>
<td>AR, CTSC, 11q14, allelic to Papillon–Lefèvre syndrome</td>
<td>Onychogryphosis of thumbs and great toe</td>
<td>Normal</td>
<td>Hyperkeratosis after extending onto dorsum of hands and feet and on extensor area of arms and legs</td>
<td>Periodontitis</td>
<td>–</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Keratoderma palmoplantar punctate type I, keratoderma palmoplantaris papulosa of Buschke–Fischer [64, 333, 334]</td>
<td>AR, AAGAB, 15q22-q24</td>
<td>Subungual hyperkeratosis, onychogryphosis, longitudinal furrows</td>
<td>Normal</td>
<td>Papulo-verrucoid palmoplantar lesions after puberty, progressively increasing. Hyperhidrosis of palms and soles may occur as well as hyperkeratosis of knees</td>
<td>Normal</td>
<td>–</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Keratoderma with leukonychia totalis [335, 336]</td>
<td>AD?, probably allelic to Bart–Pumphrey syndrome</td>
<td>Leukonychia totalis</td>
<td>Coiled with furrows. Trichorhexis nodosa</td>
<td>Follicular hyperkeratosis</td>
<td>Transversal furrows of incisors</td>
<td>Deafness</td>
<td>–</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Keratoderma palmoplantar mutilans with deafness (Vohwinkel syndrome) [337–340]</td>
<td>AD, GJB2, 13q11-q12, LOR, 1q21</td>
<td>Pseudoainhum</td>
<td>Alopecia</td>
<td>Papular keratoderma, mild honeycomb keratoderma, knuckle</td>
<td>Normal</td>
<td>Deafness high tones</td>
<td>–</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

(Continued)
Table 9.2 (Continued)

<table>
<thead>
<tr>
<th>Condition</th>
<th>Inheritance, gene, mapping</th>
<th>Nails</th>
<th>Hair</th>
<th>Skin changes</th>
<th>Teeth</th>
<th>Ear</th>
<th>Eye</th>
<th>Other findings</th>
</tr>
</thead>
<tbody>
<tr>
<td>Scleroylosis. PPK with atrophic fibrosis of the extremities [341–345]</td>
<td>AD, 4q23 181600</td>
<td>Hypoplastic with fracture of free edge. Longitudinal ridging, koilonychia, and complete aplasia. Transverse and increased longitudinal curvature</td>
<td>Retroauricular alopecia</td>
<td>Since birth palmpoplantar hyperkeratosis and scleroderma-like atrophy of tips of fingers and toes and over finger joints. Risk for squamous cell carcinoma.</td>
<td>Microdontia</td>
<td>–</td>
<td>–</td>
<td>Increased risk of intestinal cancer. An autosomal recessive palmpoplantar hyperkeratosis with squamous cell carcinoma of skin, 46XX sex reversal (MIM 610644), and dystrophic nails is associated with mutation of RSP1 gene (1p34.3)</td>
</tr>
<tr>
<td>Keratoderma palmpoplantar, with nail dystrophy and hereditary motor-sensory neuropathy [348]</td>
<td>AD 148360</td>
<td>Dystrophic nails at birth or early childhood with painful longitudinal cracks</td>
<td>Normal</td>
<td>Focal hyperkeratosis on palms and soles</td>
<td>Not mentioned</td>
<td>–</td>
<td>–</td>
<td>Motor and sensory neuropathy</td>
</tr>
<tr>
<td>Keratosis focal palmpoplantar and gingival hyperkeratoses syndrome [349–351]</td>
<td>AD 148730</td>
<td>Sub- and periungual hyperkeratosis</td>
<td>Normal</td>
<td>Changes marked on friction areas. Appear at age 5 on fingers. Later on toes</td>
<td>Normal</td>
<td>–</td>
<td>–</td>
<td>Gingival hyperplasia, rare and mild follicular keratosis</td>
</tr>
<tr>
<td>Keratosis, ichthyosis and deafness (KID syndrome) [352–356]</td>
<td>AD, GJB2, 13q12.11 148210</td>
<td>Thick white nails most marked on fingers</td>
<td>Hypotrichosis. Eyebrows and eyelashes absent</td>
<td>Erythrokeratodermia on knees and palms, pitted type of hyperkeratosis. Plaques on central portion of face. Hypohidrosis</td>
<td>Normal or abnormal</td>
<td>Neurosensory deafness</td>
<td>Vascularization of cornea, keratitis, photophobia, conjunctivitis, trichiasis</td>
<td>Tight heel cords may occur. Fungal infections common. Oral leukoplakia, scrotal tongue. Ichthyosis hystrix-like with deafness (MIM 602540) is an allelic form</td>
</tr>
<tr>
<td>Condition</td>
<td>Inheritance, gene, mapping</td>
<td>Nails Hair Skin changes</td>
<td>Teeth</td>
<td>Ear</td>
<td>Eye</td>
<td>Other findings</td>
<td>MIM no.</td>
<td></td>
</tr>
<tr>
<td>------------------------------------------------</td>
<td>----------------------------------------------------------------</td>
<td>-------------------------</td>
<td>-------</td>
<td>-----</td>
<td>-----</td>
<td>----------------</td>
<td>---------</td>
<td></td>
</tr>
<tr>
<td>Keratosis, ichthyosis and deafness (KID syndrome AR) [357, 358]</td>
<td>AR 242150</td>
<td>Short and fragile</td>
<td>Alopecia</td>
<td>Ichthyosis</td>
<td>Neurosensory deafness</td>
<td>Keratoconus, myopia, photophobia, conjunctivitis, decreased tearing</td>
<td>Mental retardation, failure to thrive, short stature, cirrhosis, hepatic glycogen storage</td>
<td></td>
</tr>
<tr>
<td>Naxos disease [317, 359]</td>
<td>AR, JUP, 17q21 601214</td>
<td>Curved</td>
<td>Woolly, bristly</td>
<td>Diffuse hyperkeratosis, no blisters</td>
<td>–</td>
<td>Smooth tongue, reduced fungiform and filiform papillae</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Pachyonychia congenita-K16 (PC-K16), previously pachyonychia congenita type 1 Jadassohn–Lewandowsky, pachyonychia congenita type 1 [84, 367–369]</td>
<td>AD, KRT16, 17q12-q21 167200</td>
<td>Yellow or brown at age 3–5 months, followed by thickening of nail bed. Paronychia common. Onycholysis. Thickened toenails and fingernails in 95% and 61% of patients, respectively (before the age of 14 years in 75% of patients)</td>
<td>Normal</td>
<td>Painful PPK in 99% of patients (before the age of 14 years). Might be focal. Palmpoplantar hyperkeratosis often with blisters. Follicular hyperkeratosis with hyperpigmentation Leukokeratosis of tongue.</td>
<td>Natal teeth caries or normal. Leukokeratosis (41% of cases)</td>
<td>Deafness</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Pachyonychia congenita-K17 (PC-K17), previously pachyonychia congenita type 2 of Jackson and Lawler [370–373]</td>
<td>AD, KRT17, 17q12-q21 167210</td>
<td>Thick subungual hyperkeratosis at early age (before the age of 1 year in &gt;68% of patients). Affected toenails and fingernails in 99% and 87% of patients, respectively</td>
<td>Dry, kinky, sometimes alopecia</td>
<td>Painful PPK in 80% of patients (occurs before the age of 14 years in 90% of cases). Palmoplantar hyperhidrosis. Follicular keratosis (69%). Pilosebaceous cysts (92%)</td>
<td>Natal teeth (76% of cases). Leukokeratosis (27% of cases)</td>
<td>–</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

(Continued)
<table>
<thead>
<tr>
<th>Condition</th>
<th>Inheritance, gene, mapping</th>
<th>Nails</th>
<th>Hair</th>
<th>Skin changes</th>
<th>Teeth</th>
<th>Ear</th>
<th>Eye</th>
<th>Other findings</th>
</tr>
</thead>
<tbody>
<tr>
<td>Pachyonychia congenita-K6A (PC-K6A) or PC3</td>
<td>AD, KRT6A, 12q13, 615726</td>
<td>Thick subungual hyperkeratosis at early age (before the age of 4 years in 98% of patients). Affected toenails and fingernails (99% of the patients)</td>
<td></td>
<td>Patients have PPK (89%) and pain (96%) (occur before the age of 14 years in 99% of cases). Palmoplantar hyperhidrosis. Follicular keratosis (61%). Pilosebaceous cysts (68%)</td>
<td>Natal teeth (2% of cases). Leukokeratosis (88% of cases)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Pachyonychia congenita-K6B (PC-K6B) or PC4</td>
<td>AD, KRT6B, 12q13, 615728</td>
<td>Thick subungual hyperkeratosis at early age (before the age of 14 years in 84% of patients). Affected toenails and fingernails in 98% and 50% of the patients, respectively</td>
<td></td>
<td>Patients have PPK (96%) and pain (100%) (occur after the age of 5 years in 97% of cases). Palmoplantar hyperhidrosis. Follicular keratosis (46%). Pilosebaceous cysts (72%)</td>
<td>No natal teeth. Leukokeratosis (30% of cases)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Pachyonychia congenita-K6C (PC-K6C)</td>
<td>AD, KRT6C, 12q13, 615735</td>
<td>Thick subungual hyperkeratosis of less than 6 toenails. Fingernails are rarely involved (occur before the age of 14 years in 90% of cases)</td>
<td></td>
<td>Patients have PPK (94%) and pain (100%) (occur after the age of 14 years in 100% of cases). Might be focal. Palmoplantar hyperhidrosis. Follicular keratosis is not reported. Pilosebaceous cysts (24%)</td>
<td>No natal teeth. Leukokeratosis (18% of cases)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Condition</td>
<td>Inheritance</td>
<td>Gene/Region</td>
<td>Mapping</td>
<td>Nails</td>
<td>Hair</td>
<td>Skin</td>
<td>Other findings</td>
<td>MIM no.</td>
</tr>
<tr>
<td>------------------------------------------------</td>
<td>-------------</td>
<td>-------------</td>
<td>-----------------------</td>
<td>-------</td>
<td>------</td>
<td>------</td>
<td>-----------------------------------------------------</td>
<td>-----------------</td>
</tr>
<tr>
<td>Pachyonychia congenita with leukonychia [376]</td>
<td>AR</td>
<td>260130</td>
<td></td>
<td>–</td>
<td>–</td>
<td>–</td>
<td>–</td>
<td>–</td>
</tr>
<tr>
<td>Peeling skin with leukonychia, acral punctate keratoses, cheilitis, and knuckle pads (PLACK syndrome) [377]</td>
<td>AR, CAST, 5q15</td>
<td>616295</td>
<td>Proximal leukonychia, mild distal onycholysis</td>
<td>–</td>
<td>–</td>
<td>–</td>
<td>Generalized peeling skin, acral punctate keratosis, PPK, knuckle pads, hyperkeratotic micropapules over dorsum of interphalangeal joints</td>
<td>–</td>
</tr>
<tr>
<td>Poikiloderma, bullous. Kindler syndrome (see Table 9.9) [378–380]</td>
<td>AR, KIND1, 20p12.3</td>
<td>173650</td>
<td>Dystrophic</td>
<td>Normal</td>
<td>Normal</td>
<td>Normal</td>
<td>Poikiloderma gradually appearing with cutaneous atrophy and reticulated pigmentation. Friction blisters in infancy. Hyperkeratosis of palms and soles, often mild</td>
<td>–</td>
</tr>
<tr>
<td>Poikiloderma, acrokeratotic. Weary syndrome or hereditary sclerosing [381–383]</td>
<td>AD</td>
<td>173700</td>
<td>Dystrophic</td>
<td>Normal</td>
<td>Normal</td>
<td>Normal</td>
<td>Vesiculo-pustules on hands and feet. Dermatitis. Reticulated pigmentation without telangiectasia or severe atrophy. Sparse on head. Keratotic papules of dorsal hands, feet, elbows, and knees. Sometimes also on palms and soles</td>
<td>Poor dentition can occur</td>
</tr>
<tr>
<td>Poikiloderma with neutropenia, Clericiuzio type [384–386]</td>
<td>AR, C16orf57, 16q21</td>
<td>604173</td>
<td>Dykeratotic. Thickening predominates on the toenails</td>
<td>Normal</td>
<td>Normal</td>
<td>Normal</td>
<td>Poikiloderma begins in middle infancy, as punctiform edematous papules or eczematous lesions. Telangiectatic lesions occur later. Lesions start on limbs and frequently spare the trunk</td>
<td>Recurrent pneumonias. Neutropenia may be cyclical, neonatal hypoglycemia, thrombocytopenia, delayed maturation of the biliary plate, muscle involvement (intermittent elevation of creatine kinase)</td>
</tr>
<tr>
<td>Condition</td>
<td>Inheritance, gene, mapping</td>
<td>Nails</td>
<td>Hair</td>
<td>Skin changes</td>
<td>Teeth</td>
<td>Ear</td>
<td>Eye</td>
<td>Other findings</td>
</tr>
<tr>
<td>------------------------------------------------</td>
<td>---------------------------</td>
<td>----------------------------</td>
<td>-------------------------------------</td>
<td>-----------------------------------</td>
<td>---------------------------</td>
<td>------------------------------</td>
<td>------------------------------</td>
<td>-----------------------------------------------------</td>
</tr>
<tr>
<td>Rosselli–Gulinetti syndrome [387, 388]</td>
<td>AR 225000</td>
<td>Onychodysplasia is reported</td>
<td>Sparse eyelashes and eyebrows</td>
<td>Abnormal hair</td>
<td>Hypodontia, anodontia, microdontia</td>
<td>Antverted ears</td>
<td>Normal</td>
<td>Abnormal philtrum, cleft lip/palate, cutaneous syndactyly, psychomotor retardation possible</td>
</tr>
</tbody>
</table>

Inheritances are indicated as follows: AD, autosomal dominant; AR, autosomal recessive; XD, sex-linked dominant; XR, sex-linked recessive; ?, still unclear.

EEG, electroencephalogram.
Involvement of other organs include the kidney and the eye. Renal involvement is seen in 42% of cases with various degrees of dysfunction [48, 49]. Renal changes have recently been described as the only manifestation of the syndrome [50–52]. The presence of collagen-like fibrils in the glomerular basement membrane as revealed by electron microscopy is diagnostic [53]. The renal symptoms are usually first discovered in adults as asymptomatic proteinuria. The end result can be a nephrotic-like picture, which can result in renal failure.

Heterochromia of the iris with hyperpigmentation of the papillary margin are often helpful diagnostic signs. In addition, microcornea and glaucoma have been reported. More rare signs include webs on the fingers and pterygia in the popliteal or antecubital areas [54], cutis laxa, and palmoplantar hyperhidrosis [55]. Missing creases in the skin overlying the distal interphalangeal joints are reported as a diagnostic clue by Itin et al. [56].

The syndrome is inherited as an autosomal dominant trait. The LMX1B gene is located on chromosome 9q33.3 [57].

### Ectodermal dysplasias

The term ectodermal dysplasia (ED) was introduced by Weech [58]. It is used to cover a heterogeneous group of primary epidermal disorders in which at least one of the following signs occur: hypotrichosis, hypodontia, onychodysplasia, and anhidrosis, plus at least one sign affecting other structures of epidermal origin as classified by Freire-Maia [59] and Freire-Maia and Pinheiro [60]. Solomon and Kcuer [61] prefer to exclude diseases that are progressive. The list of ED now includes over 187 different conditions [62]. Whether there is a reduction in sweating in certain areas has in many cases not been fully tested, which makes this part of the classification weak [63]. It is therefore preferential to list skin changes instead of hidrotic changes. Additional ectodermal tissues which can be involved are ears, lens of the eyes, anterior pituitary gland, central nervous system, and adrenal medulla. Other embryological germ layers may also be involved, but when they dominate and when epidermal changes are secondary they are not considered as ED.

Tables 9.2–9.4 list the combinations and features where the nails are involved. Since thickening of the soles and palms is an easily recognized sign, those with palmoplantar keratoderma (PPK) have been grouped together (Table 9.2). The various types of PPK have been reviewed by Stevens et al. [64]. Here we have included only those with nail changes. The nail changes in other EDs with changes of teeth and hair or skin are listed in Table 9.3, and those in which the teeth are normal in are listed in Table 9.4. Four important conditions listed in Tables 9.2–9.4 are described in the following sections.

### Hypohidrotic ectodermal dysplasia

Charles Darwin [65] first described a Hindu family with ED of X-linked type; today this is called Christ–Siemens–Touraine syndrome [66–68]. Rare autosomal recessive and dominant types are reported [69–71]. The prominent features are the typical facies, often with a depressed nasal bridge (saddleback nose), large and conspicuous nostrils, high cheek bones, and a narrow lower face. The eyebrows are scanty and the eyes slant upward. The lips can be thick and the buccal commissures have radiating furrows. Sebaceous gland hyperplasia and telangiectasias are often seen on the cheeks. The hair of the scalp and body is thin and sparse. There is hypodontia, reduced sweating, and decreased function of the lacrimal ducts. The nails can be normal, fragile, dystrophic, or absent at birth (Figs 9.11–9.15). A combination with hypothyroidism and ciliary dyskinesia was described by Pabst et al. [72]. Other syndromes are described where cleft lip and palate dominate the picture, Rapp–Hodgkin syndrome, or ankyloblepharon–ectodermal–cleft (AEC) syndrome and ectrodactyly–ectodermal clefting (EEC) syndrome. Genitourinary anomalies can also occur with these syndromes [73–76], which are related to TP63 gene mutations (Table 9.2).

### Pachyonychia congenita

Pachyonychia congenita is a hereditary ED with thickening of the nails and subungual hyperkeratosis appearing within the first 6 months of life but late onset has also been reported [77, 78]. There is also abnormal keratinization of skin and mucosa membranes.

Nail changes associated with keratosis of the palms and soles were mentioned in the literature from the seventeenth and eighteenth centuries [79] and were well described in a thesis by the Danish physician Musaeus [80]. Colcott-Fox [81], Müller [82], and Garrick-Wilson and Cantab [83] also reported the condition. The following...
Table 9.3 Ectodermal dysplasias (EDs) with nail and teeth changes: hair and skin often involved.

<table>
<thead>
<tr>
<th>Condition</th>
<th>Inheritance, gene, mapping</th>
<th>Nails</th>
<th>Hair</th>
<th>Skin</th>
<th>Teeth</th>
<th>Ear</th>
<th>Eye</th>
<th>Other findings</th>
</tr>
</thead>
<tbody>
<tr>
<td>AEC syndrome [74, 290, 395, 396], Limb– mammary syndrome (MIM 603543) is included</td>
<td>AD, TP63, 3q28 106260</td>
<td>Absent or dystrophic</td>
<td>Partial or complete loss</td>
<td>Dry. Partial anhidrosis, often thick palms and soles. Hidrocystoma</td>
<td>Widely spaced</td>
<td>Auricular deformities common</td>
<td>Ankyloblepharon. Lacrimal duct atresia</td>
<td>Cleft lip and palate. Syndactyly, supernumerary nipples. Adhesions between jaws can occur</td>
</tr>
<tr>
<td>ADULT (acro-dermatolyallucal-tooth syndrome) [397, 398]</td>
<td>AD, TP63, 3q28 103285</td>
<td>Concave dysplastic</td>
<td>Blond, thin scalp, sparse axillary, premature hair loss (&gt;30 years)</td>
<td>Atrophic, thin, dry, and photosensitive. Freckling</td>
<td>Hypodontia, oligodontia, small teeth, premature loss</td>
<td>–</td>
<td>Conjunctivitis, lacrimal duct obstruction</td>
<td>Breast hypoplasia, absent or hypoplastic and widely spaced nipples, mammary gland hypoplasia</td>
</tr>
<tr>
<td>Acrorenal (AREDYLD) syndrome)</td>
<td>AR? 207780</td>
<td>Transverse and longitudinal grooves of fingernails</td>
<td>Hypotrichosis. Slow growing</td>
<td>Reduced sweating</td>
<td>Hypodontia, anodontia</td>
<td>–</td>
<td>–</td>
<td>Lipodystrophic diabetes and hypomastia. Unusual face</td>
</tr>
<tr>
<td>Ectodermal dysplasia type 8 [401]</td>
<td>AR, ?, 18q22 602401</td>
<td>Dystrophic fingernails and toenails. Thin, flat fingernail plates</td>
<td>Thin body hair. Fine and thin scalp hair. Sparse scalp hair (in some patients). Sparse or absent eyebrows and eyelashes</td>
<td>Normal sweating</td>
<td>Misshapen teeth. Large, irregular, and missing teeth</td>
<td>–</td>
<td>–</td>
<td></td>
</tr>
<tr>
<td>Coffin–Siris syndrome [38, 39, 406–408]</td>
<td>AD, ARID1A, ARID1B, SMARCA4, SMARCB1, SMARCE1, 1p36, 6q25, 19p13, 22q11, 17q21 614607, 135900, 614609, 614608, 616938</td>
<td>Fifth finger and toenails hypoplastic or absent, other nails sometimes hypoplastic</td>
<td>Sparse on scalp, eyebrows, and lashes. Hirudism of limbs, forehead, and back</td>
<td>Dermatoglyphic changes</td>
<td>Delayed eruption. Microdontia</td>
<td>–</td>
<td>–</td>
<td>Thick lips. Low nasal bridge. Microcephaly. Psychomotor and growth retardation. Absence or hypoplasia of distal phalanges, especially of fifth finger and fifth toe. Patellar dysplasia. Respiratory infections. Majority of cases are female (85%). Differential diagnosis might be discussed in female patients carrying PHEF gene de novo mutation (XRF disease) presenting with hypoplastic nail of the fifth digit [238, 359]</td>
</tr>
<tr>
<td>Condition</td>
<td>Inheritance</td>
<td>Findings</td>
<td>Genes</td>
<td>Imaging and Other Features</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>------------------------------------------------</td>
<td>-------------</td>
<td>--------------------------------------------------------------------------</td>
<td>----------------------------------------------------------------------</td>
<td>------------------------------------------------------------------</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Congenital hypoparathyroidism [409]</td>
<td></td>
<td>Malocclusion, caries, Loss of enamel</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Dentooculocutaneous syndrome or Ackerman syndrome [410]</td>
<td>AR 200970</td>
<td>Horizontal ridging with distal onychoschizia</td>
<td>EDA1, Xq12-q13</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Ectodermal dysplasia with distinctive facial appearance, alopecia, and polydactyly</td>
<td></td>
<td>Scanty, no beard</td>
<td>Indurated and hyperpigmented over finger joints</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Fried's tooth and nail syndrome [411]</td>
<td>AR 129540</td>
<td>Normal</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Hay–Wells syndrome: see AEC syndrome</td>
<td></td>
<td>Thin on finger. On toes: also small and concave</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Hypohidrotic ED</td>
<td></td>
<td>Thin, dry, shiny. No or decreased sweating.</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Hypohidrotic ED (type 12) [418]</td>
<td>AD, KDF1, 1p36 617337</td>
<td>Small, concave koilonychia, sometimes rapid growing</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Hypohidrotic ED (type 12) [418]</td>
<td></td>
<td>Thin and sparse</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Hypohidrotic ED (type 12) [418]</td>
<td></td>
<td>Mild hypohidrosis, intolerance to heat</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>Delayed eruption.</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>Adontia, hypodontia, or normal teeth</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>Ocular dryness, mild photophobia</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>As above</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Condition</td>
<td>Inheritance, gene, mapping</td>
<td>Nails</td>
<td>Hair</td>
<td>Skin</td>
<td>Teeth</td>
<td>Ear</td>
<td>Eye</td>
<td>Other findings</td>
</tr>
<tr>
<td>-----------</td>
<td>---------------------------</td>
<td>-------</td>
<td>------</td>
<td>------</td>
<td>-------</td>
<td>-----</td>
<td>-----</td>
<td>----------------</td>
</tr>
<tr>
<td>Nail, tooth, ear syndrome. See also DOOR syndrome (Table 9.4) [426, 427]</td>
<td>AD, ATP6B2, 8p21 124480</td>
<td>Hypoplastic and dysplastic with furrows and cracks</td>
<td>Normal</td>
<td>Chloride increased in sweat</td>
<td>Partial anodontia coniform</td>
<td>Sensory deafness</td>
<td>–</td>
<td>Syndactyly. Polydactyly may occur</td>
</tr>
<tr>
<td>Oculo-trichodysplasia (OTD) syndrome [432]</td>
<td>AR 257960</td>
<td>Fragile, brittle</td>
<td>Hypohidrosis</td>
<td>Normal</td>
<td>Small, widely spaced</td>
<td>–</td>
<td>–</td>
<td>Retinitis pigmentosa</td>
</tr>
<tr>
<td>Odontomicroonychial dysplasia [434]</td>
<td>AR 601319</td>
<td>Slow growing, short, thin</td>
<td>Normal</td>
<td>Normal</td>
<td>Precocious eruption of primary and secondary teeth with short roots</td>
<td>–</td>
<td>–</td>
<td>–</td>
</tr>
</tbody>
</table>
# Odontoonychodosplasia

<table>
<thead>
<tr>
<th>Condition</th>
<th>Inheritance</th>
<th>Gene</th>
<th>Mapping</th>
<th>Nails</th>
<th>Hair</th>
<th>Skin</th>
<th>Teeth</th>
<th>Ear</th>
<th>Eye</th>
<th>Other Findings</th>
</tr>
</thead>
<tbody>
<tr>
<td>Odontoonychodosplasia with alopecia [435, 436]. May be allelic to odontoonychodermal dysplasia (see Table 9.2)</td>
<td>AR</td>
<td>Fragile and brittle with a subungual corneal layer</td>
<td>Almost total alopecia. Absent axillary and pubic hair. Abnormal dermatoglyphics</td>
<td>Hypohidrosis</td>
<td>Micro- and hypodontia. Widely spaced teeth with hypoplastic enamel</td>
<td>--</td>
<td>Blepharitis, photophobia</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Variant of above [447]</td>
<td>AD</td>
<td>As above. Nail fold thick</td>
<td>Fine and brittle</td>
<td>Reduced palmar sweat duct potency</td>
<td>As above</td>
<td>Big ears</td>
<td>Mental retardation</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

(Continued)
<table>
<thead>
<tr>
<th>Condition</th>
<th>Inheritance, gene, mapping</th>
<th>Nails</th>
<th>Hair</th>
<th>Skin</th>
<th>Teeth</th>
<th>Ear</th>
<th>Eye</th>
<th>Other findings</th>
</tr>
</thead>
<tbody>
<tr>
<td>Tricho-odontonychial dysplasia [453]</td>
<td>AR 275450</td>
<td>Thin, concave first and third digit. Toenail dystrophic</td>
<td>Thin and dry</td>
<td>Normal sweating. Dry skin</td>
<td>Widely spaced first teeth. Most permanent teeth absent except conical incisors</td>
<td>–</td>
<td>–</td>
<td>Probably subtype of Frieds or Wickops type</td>
</tr>
<tr>
<td>Triphalangy of thumbs and toes. Possible DDOD syndrome [463]</td>
<td>AD, ATP6V1B2, 8p21.3 124480</td>
<td>Hypoplastic, absent, small, fissured, or dystrophic</td>
<td>–</td>
<td>Normal</td>
<td>Selective tooth agenesis, coniform teeth</td>
<td>Hearing loss, sensorineural</td>
<td>–</td>
<td>Brachydactyly, finger-like thumbs, triphalangeal thumbs (in some patients), short terminal phalans of the fifth finger, aplasia of middle phalans of fifth finger, bulbous swelling of the fingertips, syndactyly of toes and hypoplasia or absence of the terminal phalanges of the feet</td>
</tr>
<tr>
<td>Triphalangy of thumbs and toes. Could be same as DOOR syndrome (Table 9.2) [427]</td>
<td>AR, TBC1D24, 16p13.3 220500</td>
<td>Hypoplastic</td>
<td>Normal</td>
<td>Dermatoglyphic abnormalities</td>
<td>Widely spaced. Poorly formed</td>
<td>–</td>
<td>–</td>
<td>Three phalanges in both thumbs and great toes. Hypoplasia of distal phalanges</td>
</tr>
<tr>
<td>Xeroderma, talipes, and enamel defect (XTE) syndrome [464]</td>
<td>AR –</td>
<td>Small malformed</td>
<td>Dry, slow growing. No lower lashes</td>
<td>Hyposidrosis</td>
<td>Yellow enamel</td>
<td>–</td>
<td>Photophobia</td>
<td>Clubfoot. Oligophrenia</td>
</tr>
</tbody>
</table>

Inheritances are indicated as follows: AD, autosomal dominant; AR, autosomal recessive; XR, sex-linked recessive; ?, still unclear.
Jadassohn and Lewandowsky [84] described the full syndrome in two siblings. Feinstein et al. [85] classified pachyonychia congenita into four clinical types with increasing symptoms. In some cases only the nails are affected [86–95]. The inheritance is usually autosomal dominant, although an autosomal recessive form has been described (Table 9.2).

Initially divided into PC1 and PC2, a new classification proposes five subtypes, each corresponding to the involved keratin, i.e. PC-K6a, PC-K6b, PC-K6c, PC-K16, and PC-K17. Toenail dystrophy is one of the characteristics. The clinical appearance frequently shows the V-shaped thickening involving the hallux and the fifth toenail (role of trauma). At birth, about half of the neonates had changes occurring in the toenail. During the first year, the dystrophy of finger and toenails occurs in most of the affected infants. The PPK, often painful, is seen in two-thirds of the patients by the time they are 5 years old. The combination of age of onset, presence of PPK, concomitant involvement of toe and fingernails, and mucous membrane manifestations might help to classify pachyonychia congenita. Nail dystrophy at birth, especially involving all the nails, predicts PC-K6a or PC-K17. The occurrence of natal teeth indicates PC-K17, while hoarseness and leukokeratosis during the first year indicate PC-K6a. PC-K16 is characterized by the development of PPK during childhood with late onset of other characteristic features. Localized nail involvement is common in PC-K6c.

The differential diagnosis of pachyonychia congenita includes epidermolysis bullosa, onychogryphosis, psoriasis, and oral thrush, but the presence of thick wedge-shaped, pinched-up, or claw-like nails with yellowish-brown pigmentation together with other symptoms rarely offers any diagnostic problems.

Treatment with retinoids has been tried with, as a rule, only moderate improvement of skin and nail lesions, but positive results have also been reported [96]. Distal avulsion with nail bed scarification and matrix destruction is
### Condition

<table>
<thead>
<tr>
<th>Condition</th>
<th>Inheritance, gene, mapping</th>
<th>Nails</th>
<th>Hair</th>
<th>Skin</th>
<th>Teeth</th>
<th>Ear</th>
<th>Eye</th>
<th>Other findings</th>
</tr>
</thead>
<tbody>
<tr>
<td>Aplasia cutis congenita. See focal dermal hypoplasia</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Aplasia cutis with dystrophic nails [465, 466]</td>
<td>AD 107600</td>
<td>Short, thin, gray nail plate. Longitudinal stria. Some onychogryphotic</td>
<td>Normal</td>
<td>Aplasia cutis of scalp and/or trunk</td>
<td>Normal</td>
<td>–</td>
<td>–</td>
<td></td>
</tr>
<tr>
<td>Apical dysplasia of fingers [467]</td>
<td>AD</td>
<td>Transverse depressions</td>
<td>Normal</td>
<td>Epidermal dysplastic ridges. Fingerpads hypoplastic with painful chaps</td>
<td>Normal</td>
<td>–</td>
<td>–</td>
<td></td>
</tr>
<tr>
<td>Atrichia with nail dystrophy syndrome IFAP ? [468]</td>
<td>AR</td>
<td>Distal parts dystrophic and brittle</td>
<td>Alopecia. A few pigmented short hairs on scalp. Eyebrows and lashes sparse</td>
<td>Normal</td>
<td>Normal</td>
<td>–</td>
<td>–</td>
<td>Moderate retardation with delayed speaking. Abnormal facies with depressed nasal bridge, hypertelorism, and long philtrum</td>
</tr>
<tr>
<td>CHANDS syndrome (curly hair, ankyloblepharon, nail dysplasias) [469, 470]</td>
<td>AR 214350</td>
<td>Small, hypoplastic</td>
<td>Curly</td>
<td>Normal</td>
<td>Normal</td>
<td>–</td>
<td>Ankyloblepharon Ataxia</td>
<td></td>
</tr>
</tbody>
</table>

Table 9.4 Ectodermal dysplasia (ED) with hair and/or skin changes but without dental changes.
<table>
<thead>
<tr>
<th>Disorder Description</th>
<th>Inheritance</th>
<th>Eye Findings</th>
<th>Scalp Hair Findings</th>
<th>Scalp Skin Findings</th>
<th>Other Findings</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>AD ?129200</td>
<td>Transverse overcurvature, irregular, atrophic</td>
<td>Papillary ridging lacking.</td>
<td>Normal</td>
<td>Psychomotor and growth retardation.</td>
</tr>
<tr>
<td></td>
<td></td>
<td>with central fissures and ridging</td>
<td>Abnormal furrows of hands</td>
<td></td>
<td>Frontal bossing. Depressed bridge of the nose.</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>ED with short stature [484]</td>
<td>AR, GRHL2,</td>
<td>Dystrophic, absent</td>
<td>Sparse in focal areas of scalp and palms</td>
<td>Normal or enamel defects</td>
<td>Hyperpigmentation of the oral mucosa.</td>
</tr>
<tr>
<td></td>
<td>8q22.3</td>
<td></td>
<td></td>
<td></td>
<td>Hyperpigmentation of the tongue.</td>
</tr>
<tr>
<td></td>
<td>646029</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>Xp11.23</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>305600</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>ED hair–nail type 4 [488]</td>
<td>AR, KRT85,</td>
<td>Onychodystrophy, micronychia, onycholysis</td>
<td>Alopecia, absent</td>
<td>Normal</td>
<td></td>
</tr>
<tr>
<td></td>
<td>12q13</td>
<td></td>
<td>body hair, eyebrows and eyelashes.</td>
<td>Normal</td>
<td></td>
</tr>
<tr>
<td></td>
<td>602032</td>
<td></td>
<td>Brittle hair. Pili torti.</td>
<td>Normal</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>Sparse body hair (in some patients)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>ED hair–nail type 5</td>
<td>AR, ?,</td>
<td>Micronychia, dystrophic fingernails, anonychia</td>
<td>Thin scalp hair, fine eyebrows, fine eyelashes, thin</td>
<td>Normal</td>
<td></td>
</tr>
<tr>
<td></td>
<td>10q24.32-q25.1</td>
<td>of fingernails and toenails</td>
<td>body hair</td>
<td>Normal</td>
<td></td>
</tr>
<tr>
<td></td>
<td>614927</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>ED hair–nail type 6</td>
<td>AR, ?,</td>
<td>Koilonychia of fingernails and toenails, thin or</td>
<td>Total alopecia at birth, curly, sparse hair on the</td>
<td>Normal</td>
<td></td>
</tr>
<tr>
<td></td>
<td>17p12-q21.2</td>
<td>dystrophic toenails</td>
<td>scalp at 5 years of age, hair can be painlessly</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>614928</td>
<td></td>
<td>plucked without force</td>
<td></td>
<td></td>
</tr>
<tr>
<td>ED hair–nail type 7</td>
<td>AR, KRT74,</td>
<td>Dystrophic fingernails and toenails. Micronychia,</td>
<td>Total alopecia at birth, hypotrichosis, brittle hair.</td>
<td>Normal</td>
<td></td>
</tr>
<tr>
<td></td>
<td>12q13.13</td>
<td>onycholysis</td>
<td></td>
<td>Normal</td>
<td></td>
</tr>
<tr>
<td></td>
<td>614929</td>
<td></td>
<td></td>
<td>Normal</td>
<td></td>
</tr>
</tbody>
</table>

(Continued)
<table>
<thead>
<tr>
<th>Condition</th>
<th>Inheritance, gene, mapping</th>
<th>Nails</th>
<th>Hair</th>
<th>Skin</th>
<th>Teeth</th>
<th>Ear</th>
<th>Eye</th>
<th>Other findings</th>
</tr>
</thead>
<tbody>
<tr>
<td>ED hair–nail type 9 [490]</td>
<td>AR, HOXC13, 12q13.13</td>
<td>Dystrophic nails, koilonychia, micronyenia</td>
<td>Hypotrichosis, atrichia</td>
<td>Normal</td>
<td>Normal</td>
<td>Normal</td>
<td>Normal</td>
<td>Nipple and breast hypoplasia</td>
</tr>
<tr>
<td>Finlay–Marks syndrome, scalp–ear–nipple syndrome [491]</td>
<td>AD, KC1D1, 18q11.2</td>
<td>Brittle fingernails</td>
<td>Scanty secondary sexual hair, reduced axillary hair</td>
<td>Congenital denuded scalp areas, reduced axillary apocrine secretion</td>
<td>Widely spaced, missing secondary teeth</td>
<td>Small/ rudimentary tragus, antitragus, and lobules. Cupped ears, protruding ears</td>
<td>Normal</td>
<td>Absence of skin defect</td>
</tr>
<tr>
<td>Hyper- and hypopigmentation with dystrophic nails [493]</td>
<td>AD, 22q11.1</td>
<td>Thin, brittle with longitudinal furrows</td>
<td>Normal</td>
<td>Symmetrical pigmentation and hyperkeratosis of non-exposed skin with areas of hypopigmentation</td>
<td>Normal</td>
<td>Normal</td>
<td>Normal</td>
<td>Normal</td>
</tr>
<tr>
<td>Pili torti and onychodysplasia. Could be a form of ED pure hair–nail type [498]</td>
<td>AR, 18q11.2</td>
<td>Dystrophy of distal part.</td>
<td>Scalp, beard, pubic and axillary hair broken at 1–10 mm length. Eyebrows, eyelashes, and body hair absent</td>
<td>Normal</td>
<td>Normal</td>
<td>Normal</td>
<td>Normal</td>
<td>Facial dysmorphism with long philtrum</td>
</tr>
<tr>
<td>Condition</td>
<td>Inheritance</td>
<td>Detriment</td>
<td>Other Findings</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>-----------</td>
<td>-------------</td>
<td>-----------</td>
<td>----------------</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Retinal angiomias with hair and nail defects [499]</td>
<td>AR</td>
<td>Dysplastic</td>
<td>Normal</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Thumb deformation and alopecia [500, 501]</td>
<td>AD 188150</td>
<td>–</td>
<td>Alopecia</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Tricho-oculodermal vertebral syndrome or arthrogryposis and ED [502, 503]</td>
<td>AR 601701</td>
<td>Thin and brittle fingernails. Toes wide and short with paronychia</td>
<td>Hypotrichosis Dry and rough</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Tricho-iodystrophy, non-photosensitive [113, 504–506] or TTD4 (for MPLKIP), TTD5 (for RNF113A), and TTD6 (for GTF2E2)</td>
<td>AR, XLR MPLKIP (or C7orf11), RNF113A, GTF2E2, 7p14, Xq26, 8p12 234050, 300953, 616943</td>
<td>Break easily. Do not grow long</td>
<td>Brittle, short, trichoschisis, trichorrhexis nodosa in some</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Tricho-iodystrophy, photosensitive (TTD) or Tay syndrome [111] or TTD1 (for ERCC2), TTD2 (for ERCC3) and TTD3 (for GTF2H5)</td>
<td>AR, ERCC2, ERCC3, GTF2H5, 19q13, 2q14, 6q25 3, 601675, 616390, 616395</td>
<td>Brittle and dystrophic or thick, convex curvature, subungual hyperkeratosis. Elsewhere hypoplastic or dystrophic with spotted leukonychia and lamellar splitting</td>
<td>Brittle, short, trichoschisis, trichorrhexis nodosa in some</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Tricho-iodystrophy with transient immunodeficiency [507]</td>
<td>–</td>
<td>Short with horizontal splitting. Thin and often spoon shaped</td>
<td>Normal</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Inheritances are indicated as follows: AD, autosomal dominant; AR, autosomal recessive; XD, sex-linked dominant transmission; XR, sex-linked recessive.

BIDS, brittle hair, impaired intelligence, decreased fertility and short stature; DOOR, deafness, onychosteedystrophy, mental retardation; IBIDS, ichthyosis, brittle hair, impaired intelligence, decreased fertility and short stature; IFAP, ichthyosis follicularis–alopecia–photophobia; PIBIDS, photosensitivity, ichthyosis, brittle hair, impaired intelligence, decreased fertility and short stature.
needed to prevent the growth of nails. Areas of ulceration should be observed for possible skin malignancy [97]. Specific therapy using siRNA was successfully performed in pachyonychia congenita [98].

Dyskeratosis congenita

Short and atrophic fingernails appearing after late childhood is characteristic of dyskeratosis congenita (DC) (Fig. 9.18). X-linked recessive and autosomal recessive cases have a high incidence of nail dystrophy skin changes and leukoplakia with earlier presentation (median is 15 years). Autosomal dominant cases are usually milder, and may present later (third decade) of life. The nail (98%) can initially be thin, concave with longitudinal ridging and pterygium [99], and the changes may progress to loss of nails. Some patients may be thought...
to have twenty-nail dystrophy. At the same time crops of vesicles appear in the mouth, which ulcerate and leave an atrophic mucosa. There is palmar hyperkeratosis and hyperhidrosis and almost always a reticulated hyperpigmentation of the face, neck, and chest. The complete syndrome is not apparent until the second or third decade of life [100–102]. Continuous lacrimation due to atresia of the lacrimal duct and thickened fissured mucosal leukoplaeka is common not only in the mouth but also in the esophagus, anus, urethra, and vagina. There is a high risk of developing early malignancy in these lesions and frequent biopsies are often needed. Dental caries and early loss of teeth are seen. The eye manifestations are epiphora, fundus changes, blepharitis, and loss of eyelashes. The ear manifestations include transparent tympanic membrane, meatal atresia, and malformations of the middle ear. Intracranial calcification and increased fragility of bones have been reported. Abnormal immunology with hematopoietic disorders occur in 50% of patients in the second and third decades and may be the presenting changes. The manifestations include anemia, bone marrow hypoplasia, thrombocytopenia, and pancytopenia [103]. Testicular atrophy is common. Zinsser–Engman–Cole syndrome corresponds to the X-linked form of the disorder. Both autosomal dominant and recessive forms of the disorder have been reported. Several genes are involved. Hematopoietic stem cell transplantation is the standard treatment of bone marrow complications. Non-myeloablative conditioning regimens may be more successful (Table 9.2).

**Trichothiodystrophy**

Patients with trichothiodystrophy (TTD) have brittle hair and nails due to low cystine-rich matrix proteins [104]. In addition, the patients frequently have nail dystrophy with ridging, lamellar splitting, and koilonychias (Fig. 9.19), and spotted leukonychia. In one type, called Tay syndrome or IBDS (ichthyotic, brittle hair, decreased fertility, short stature) (Table 9.4) the skin is ichthyotic and the nails can also be thick with subungual hyperkeratosis [105]. The palms and soles could be thickened and fissured, but keratoderma was not mentioned in the review of 95 cases by Itin and Pittelkow [106].
TTD is recessively inherited. Three genetic groups are recognized. Mutations in the three genes encoding TFIIH subunits (XPD, XPB, and TTF-a/p8) are responsible for the in vitro photosensitive form (group I) [107–109]. Group II is represented by non-photosensitive TTD; mutations in the c70rf11 gene are reported for patients in this group. The last group, group III, corresponds to the patients without known molecular basis [110, 111]. Minor dental abnormalities such as caries were mentioned in 10% of cases (Table 9.4). Itin and Pittelkow [106] described sulfur-deficient hair in a patient who also had neutropenia. Such a syndrome has been described earlier (but not examined for sulfur) as onychotrichodysplasia with neutropenia (Table 9.4) by Cantú et al. [112], Hernandez et al. [113], and Verhage et al. [114]. Light and electron microscopy show trichoschisis and absence of cuticle. Alternating light and dark bands (tiger nail pattern) are present on polaroscopy.

**Disease loci and chromosome anomalies** (Fig. 9.20)

Chromosomal localization has now been established for several genetic traits. Mapping of important disease loci has increased rapidly during recent years. As the specific genes and their products are discovered for particular disorders, disease names no longer appear in the individual chromosome tables. Syndromes with chromosome abnormalities usually have mental deficiency and dysmorphic changes as the main features together with multiple defects [1]. The nails are often convex or hypoplastic from birth. Patients with Noonan syndrome (MIM *163950) have small stature and lymphedema of the hands and feet. Short and wide nails show koilonychia and are sometimes missing. This is also true for cardiofaciocutaneous syndrome [115] (Table 9.2).

**Nail change in syndromes with predominantly skeletal anomalies**

In patients with brachydactyly, syndactyly (Figs 9.21, 9.22), zygodactyly, and polydactyly the nails are sometimes malformed or absent. When the distal phalanges
Hypoplastic or atrophic nails with skeletal anomalies

These disorders are listed in Table 9.5. In particular, in congenital onychodysplasia of the index fingers (COIF, Kikuchi syndrome) Baran [116] suggested that it was congenital and characterized by a variety of nail deformities affecting one or both index fingers (Figs 9.23–9.25), associated with bone abnormalities, such as a Y-shaped bifurcation of the distal phalanx, visible on lateral radiographs (Fig. 9.26). Such a bone abnormality may occur under both normal and abnormal nails. The defects are mainly seen on the radial side of the index fingers. Kikuchi et al. [117] related this to the smaller caliber of the artery on the radial side. Micronychia is the commonest clinical manifestation. The so-called “rolled micronychia” is a rare variant. Anonychia, hemionychogryphosis, or simple malalignment are also less frequent presentations. A deformed lunula was described by Baran and Stroud [118] (Fig. 9.25). Millman and Strier [119], in an extensive article, described nine members of one family who had the COIF syndrome; the clinical spectrum was broadened to include autosomal dominant inheritance. This syndrome was described in identical twins [120] and in a case in which both thumbnails were also involved, possibly because of an abnormal handgrip in fetal life [121]. Kitamaya and Tsukada [122] prefer the term congenital onychodysplasia because it is not only located on the index finger. They assumed that it is due to ischemic damage in embryonic life. Kikuchi syndrome has also been reported with anomaly of the great toe [123]. Isolated congenital onychodysplasia of the toenails has been observed [124, 125].

Hyperonychia, hyperplastic thick nails, onychogryphosis (Figs 9.27, 9.28)

Large nails are seen in patients with macrodactylyia due to epidermal nevus, gigantism, and various connective tissue syndromes [126]. Thick nails are common in patients with various types of keratoderma (Table 9.2) and in ichthyosiform dermatitis (Table 9.3). Schulze [127], Burg [128], and Bazex et al. [129] described families with thick and hard nails with partial onycholysis (MIM 164800) but without other anomalies. Thick nails that split into double layers (matrix doubling syndrome) on the fingers and toes were reported by Vigh and Pinter [130]. The patients also showed oculomotor paresis, debility, and external ear aplasia. Three cases of nail bed hyperkeratosis, in which the base is normal, the surface smooth, but the distal part of the nail is raised up from the nail bed by a dark friable horny mass, were described by Garrick-Wilson and Cantab [83]. A special form is pachyonychia, i.e. thickening of the nail bed with elevation of the nail plate, which occurs in pachyonychia congenita. Pachyonychia on the toes was found in patients having a rare syndrome with severe mental retardation and unusual facies together with large ears; this is
### Table 9.5 Atrophic or hypoplastic nails with skeletal anomalies.

<table>
<thead>
<tr>
<th>Disease</th>
<th>Inheritance, gene, mapping</th>
<th>Nails</th>
<th>Other symptoms</th>
</tr>
</thead>
<tbody>
<tr>
<td>Acrogeria. Gottron syndrome [508–510]</td>
<td>AD? 201200</td>
<td>Atrophic nails</td>
<td>Thin skin with senile changes limited to distal extremities</td>
</tr>
<tr>
<td>Adams–Oliver syndrome (AOS) [511]</td>
<td></td>
<td></td>
<td>ACC of the scalp vertex, terminal transverse limb defects, cutis marmorata telangiectatica congenita, possible cardiac defects</td>
</tr>
<tr>
<td>AOS1</td>
<td>AD, ARHGAP31, 3q13 100300</td>
<td>–</td>
<td>No cardiac defect</td>
</tr>
<tr>
<td>AOS2</td>
<td>AR, DOCK6, 19p13.2 614219</td>
<td>Hypoplastic, might be absent</td>
<td>Structural brain abnormalities, ocular anomalies, and intellectual disability. Possible ACC of the trunk</td>
</tr>
<tr>
<td>AOS3</td>
<td>AD, RBPJ, 4p15 614814</td>
<td>–</td>
<td>Structural brain abnormalities, ocular anomalies, and intellectual disability. Possible ACC of the trunk</td>
</tr>
<tr>
<td>AOS4</td>
<td>AR, EOGT, 3p14 615297</td>
<td>Hypoplastic, dysplastic, or aplastic toenails</td>
<td>Prominent vessels</td>
</tr>
<tr>
<td>AOS5</td>
<td>AD, NOTCH1, 9q34 616028</td>
<td>Hypoplastic, dysplastic, or aplastic toenails</td>
<td>Hemangiomata, mild terminal transverse limb defects, cardiac anomalies (&gt;45%)</td>
</tr>
<tr>
<td>AOS6</td>
<td>AD, DLLA, 5q32 616589</td>
<td>Hypoplastic toenails (some patients)</td>
<td>Tricuspid insufficiency, ventricular septal defect, truncus arteriosus</td>
</tr>
<tr>
<td>Brachydactyly with absence of middle phalanges and hypoplastic nails or brachydactyly type A5 with nail dysplasia [512, 513]</td>
<td>AD 112800</td>
<td>Hypoplasia or absence of several nails</td>
<td>Brachydactyly. Duplicated phalanges of thumbs. Sometimes syndactyly</td>
</tr>
<tr>
<td>Brachydactyly with absence of middle phalanges and hypoplastic nails or brachydactyly type A5 with nail dysplasia [462–464]</td>
<td>AD 112800</td>
<td>Hypoplasia or absence of several nails</td>
<td>Brachydactyly. Duplicated phalanges of thumbs. Sometimes syndactyly</td>
</tr>
<tr>
<td>Brachymorphism–onychodyplasia–dysphalangism (BOD) syndrome [514, 515]</td>
<td>AD 113477</td>
<td>Hypoplasia or absent, especially of the fifth digit of each extremity</td>
<td>Hypoplasia distal phalanges. Facial dysmorphism, short stature</td>
</tr>
<tr>
<td>CHARGE syndrome [516, 517]</td>
<td>AD, CHD7, 8q12; SEMA3E (7q21) for one patient 214800</td>
<td>Hypoplastic</td>
<td>Coloboma, heart anomaly, choanal atresia. Mental retardation variable severity. Genital and ear anomalies</td>
</tr>
<tr>
<td>Chondrodysplasia type Grebe [518, 519]</td>
<td>AR, GDF5, 20q11.2 200700</td>
<td>Short dysplastic on bud-like fingertips</td>
<td>Asymmetrical dysplasia of long bones, prominent forehead, hypodontia, hearing loss</td>
</tr>
<tr>
<td>COIF syndrome (see below)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Congenital hemidysplasia with ichthyosiform erythroderma and limb defects. CHILD syndrome [274, 520–525]</td>
<td>XD, NSDHL, Xq28 308050</td>
<td>Dystrophic on affected side</td>
<td>Mainly in females. Postzygotic mutation</td>
</tr>
<tr>
<td>Cleidocranial dysostosis with micrognathia, absent thumbs. Cleidocranial dysostosis with micrognathia, absent thumbs, and distal aphangia, Yunis–Varon syndrome [526–528]</td>
<td>AR, FIG4, 6q21 216340</td>
<td>Hypoplastic or absent. Short fingertips and toes</td>
<td>Microcephaly, Dandy–Walker</td>
</tr>
<tr>
<td>Craniofrontonasal dysplasia [529–533]</td>
<td>XD, EFNB1, Xq12 304110</td>
<td>Longitudinally grooved nails, hemionychia or anonychia, brittle nails</td>
<td>Hypertelorism, broad nasal root, syndactyly, craniosynostosis. Curly hair. The phenotype is complete in females. Males typically show only hypertelorism</td>
</tr>
</tbody>
</table>
## Table 9.5 (Continued)

<table>
<thead>
<tr>
<th>Disease</th>
<th>Inheritance, gene, mapping</th>
<th>Nails</th>
<th>Other symptoms</th>
</tr>
</thead>
<tbody>
<tr>
<td>Fryns syndrome, lethal syndrome with cloudy cornea, diaphragmatic and distal defects [537–541]</td>
<td>AR, PING, 18q21 (genetic heterogeneity) 29850</td>
<td>Hypoplastic and small fingernails (thumb most severely affected), absent toenails</td>
<td>Characteristic facies with broad nasal bridge, small eyes, cleft palate, distal digital hypoplasia, urogenital and neurological anomalies. Stillborn or dead shortly after birth. Hypoplasia of lungs; diaphragm, and distal bone deformation</td>
</tr>
<tr>
<td>Fuhrmann syndrome [542]</td>
<td>AR, WNT7A, 3p25.1</td>
<td>Absent/hypoplastic fingernails (thumb most severely affected), absent toenails</td>
<td>Fibular aplasia or hypoplasia, femoral bowing, and poly-, syn-, and oligodactyly</td>
</tr>
<tr>
<td>Iso–Kikuchi (COIF) syndrome, congenital onychodysplasia of the index fingers [121, 556–559]</td>
<td>AD –</td>
<td>Anonychia, micronychia, or polyonychia of index finger</td>
<td>Patella absent in 92%. Radius head small. Iliac crest exocytosis. Eyes and kidney abnormalities as well as other changes occasionally</td>
</tr>
<tr>
<td>Osteoonychodysplasia. Nail–patella syndrome [47, 56, 57, 560, 561]</td>
<td>AD, LMBX1, 9q33 161200</td>
<td>Short, narrow, fragile, changes most pronounced on the thumb where the nails might be missing. Sometimes koilonychia. Toes rarely affected. Pterygium. Lunula missing or V shaped</td>
<td>Patella absent in 92%. Radius head small. Iliac crest exocytosis. Eyes and kidney abnormalities as well as other changes occasionally</td>
</tr>
<tr>
<td>Peeling skin syndrome 1 [562]</td>
<td>AR, CDSN, 6p21.33 270300</td>
<td>Distal onycholysis</td>
<td>Pruritic or non-pruritic spontaneous superficial peeling of the skin. Sometimes accompanied by erythema or vesiculation</td>
</tr>
</tbody>
</table>
### Table 9.5 (Continued)

<table>
<thead>
<tr>
<th>Disease</th>
<th>Inheritance, gene, mapping</th>
<th>Nails</th>
<th>Other symptoms</th>
</tr>
</thead>
<tbody>
<tr>
<td>Pre- and postnatal growth retardation, mental retardation, and acral limb deficiencies [568]</td>
<td>?</td>
<td>Small, hyperconvex, and poorly keratinized</td>
<td>Facial dysmorphism</td>
</tr>
<tr>
<td>Progeroid syndrome, Petty type [574, 575]</td>
<td>?</td>
<td>Aplasia or hypoplasia</td>
<td>Pre and postnatal growth retardation, diminished subcutaneous fat, wrinkled skin, hypoplastic distal phalanges, umbilical hernia, large open anterior fontanel</td>
</tr>
<tr>
<td>Rüdiger syndrome [576]</td>
<td>AR 268650</td>
<td>Hypoplastic</td>
<td>Normal cognitive and motor development</td>
</tr>
<tr>
<td>Weaver syndrome [577–579]</td>
<td>AD, EZH2, 7q36 277590</td>
<td>Thin, deep-set nails</td>
<td>Unusual facies. Increased weight, height, and bifrontal diameter</td>
</tr>
<tr>
<td>Williams elfin facies syndrome, Williams–Beuren syndrome [583–586]</td>
<td>AD, ELN, 7q11 194050</td>
<td>Short, deep set, or brittle</td>
<td>Coarse facies, depressed nasal bridge, hoarse voice, aortic stenosis, growth deficiency, and mental retardation</td>
</tr>
</tbody>
</table>

Inheritances are indicated as follows: AD, autosomal dominant; AR, autosomal recessive; XD, sex-linked dominant; ?, still unclear.

ACC, aplasia cutis congenita; CHARGE, coloboma, heart defects, atresia choanae (also known as choanal atresia), growth retardation, genital abnormalities, and ear abnormalities; CHILD, congenital hemidysplasia with ichthyosiform nevus and limb defects.

![Figure 9.23](image-url) Types of micronychia and other dystrophies seen particularly in congenital onychodystrophy of the index fingers (COIF). (a) Polyonychia in COIF; (b) micronychia in COIF; (c) "rolled" micronychia in COIF; (d) hemionychogryphosis in COIF; (e) malalignment in COIF; (f) anonychia in COIF; (g) usual micronychia; (h) polyonychia in syndactyly; (i) polyonychia in congenital skin disease; (j) onychoheterotopia (Ohya's type) [116, 117, 119].
Hereditary and Congenital Nail Disorders

Onychogryphosis can occur with autosomal dominant inheritance, but usually appears first in early childhood [132–136]. It can also be seen with other ectodermal malformations (Tables 9.2, 9.3).

Clubbing, acropachy, Hippocratic nails (*119900)

In clubbing the nails are thick and curved. Most common are the acquired forms seen in association with pulmonary and other systemic diseases. A hereditary form of clubbing without any other symptoms has been reviewed by Fischer et al. [137] and Myers and Farquhar [138]. It has a gradual onset from puberty. The cause of
Clubbing is proliferation of connective tissue between the nail matrix and the distal phalanx [138]. It is usually not evident before early childhood. Clubbing can also be seen as a part of various syndromes, which are listed in Table 9.6.

**Table 9.6** Hereditary forms of clubbed fingernails.

<table>
<thead>
<tr>
<th>Disease</th>
<th>Inheritance, gene, mapping</th>
<th>Comments</th>
</tr>
</thead>
<tbody>
<tr>
<td>Dystelephalangy, Kirner deformity [602, 603]</td>
<td>AD</td>
<td>Distal phalange of fifth digit is curved. Sometimes with absence of middle finger.</td>
</tr>
<tr>
<td>Keratoderma palmoplantar and clubbing of nails [346, 347]</td>
<td>AD, LMNA, 1q22</td>
<td>As above plus mandibular hypoplasia. Crowding of teeth, short stature, alopecia, prominent eyes, fat deposit over abdomen. See Table 9.7.</td>
</tr>
<tr>
<td>Otoonychoperoneal syndrome [615]</td>
<td>AR</td>
<td>Enlarged fingertips, dysmorphic craniofacial features, hypoplasia of fibula, contractures of hip, knee, and ankle joints.</td>
</tr>
<tr>
<td>Hypertrophic osteoarthropathy primary autosomal dominant</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Pachydermoperiostosis autosomal recessive [618–621]</td>
<td>AD, HPGD, 4q34.1</td>
<td>Thickening and furrowing of face and scalp. Clubbing of digits, turtleshanked nails, pachydermia.</td>
</tr>
</tbody>
</table>

Inheritances are indicated as follows: AD, autosomal dominant; AR, autosomal recessive.
Stub thumb (brachydactyly type D, “murderer’s thumb”) is a rather common genetic disorder without any other defects. The overlying nail is often called “racket nail” (see Chapter 2). It is also seen in connection with the various syndromes listed in Table 9.7.

### Isolated congenital nail dysplasia

Hamm et al. [139] have described a new autosomal condition, clinically very close to restricted nail lichen planus. Histology abnormalities include a prominent

<table>
<thead>
<tr>
<th>Disease</th>
<th>Inheritance, gene, mapping</th>
<th>Comments</th>
</tr>
</thead>
<tbody>
<tr>
<td>Acrocephalosyndactyly type II, Apert–Crouzon syndrome</td>
<td>AD, FGFR2, 10q26 101200</td>
<td>Craniosynostosis. Syndactyly. Ankylosis and other skeletal deformities</td>
</tr>
<tr>
<td>Acrocephalosyndactyly type V, Pfeiffer syndrome [635–638]</td>
<td>AD, FGFR2, 10q26, FGFR1, 8p12 101600</td>
<td>Turribrachycephaly</td>
</tr>
<tr>
<td>Cranioectodermal dysplasia [646–648]</td>
<td>AR, IFT122, 3q21.3–q22.1 218330</td>
<td>Thin and short nails. Dolichocephaly, brachydactyly</td>
</tr>
<tr>
<td>Larsen syndrome autosomal dominant [655–658]</td>
<td>AD, FLNB, 3p14.3 150250</td>
<td>Stub thumbs, cylindrical fingers, flattened peculiar facies, widely spread eyes Multiple dislocations, short metacarpals. Short nails</td>
</tr>
<tr>
<td>Mandibuloacral dysplasia with type A lipodystrophy [612, 659, 660]</td>
<td>AR, LMNA, 1q22 248370</td>
<td>Club-shaped terminal phalanges. Mandibular hypoplasia, delayed cranial closure Atrophy of skin over hands and feet. Alopecia</td>
</tr>
<tr>
<td>Megalodactyly [661, 662]</td>
<td>Somatic mosaicism, PIK3CA, 3q26.32 155500</td>
<td>No familial occurrence One or two fingers markedly enlarged Proteus syndrome might be discussed</td>
</tr>
<tr>
<td>Nasodigitoacoustic syndrome or Keipert syndrome [33, 663–665]</td>
<td>AD 255980</td>
<td>Facial abnormalities. Broad distal phalanges. Deafness</td>
</tr>
<tr>
<td>Pleonosteosis or Léri syndrome [668, 669]</td>
<td>AD, 8q22.1 microduplication 151200</td>
<td>Short stature. Spade-like hand with thick palmar pads. Massive knobby thumbs Short flexed fingers. Limited joint motion with contractures With maternal imprinting</td>
</tr>
</tbody>
</table>

(Continued)
granular layer of the nail matrix and epithelial strands, and buds extending from the nail bed. Mapping on chromosome 17p13 is reported [140].

Koilonychia (spoon nails) (MIM *149300)

In koilonychia the contour is concave instead of convex. Acquired forms are often associated with anemia, thyroid dysfunction, or trauma. Familial koilonychia without other defects is rare, but the cases reported suggest autosomal dominant transmission [141–143]. Koilonychia with dominantly inherited leukonychia was described by de Graciansky and Boule [144] and Baran and Achten [145], and with leukonychia, PPK, knuckle pads, and deafness by Bart and Pumphrey [146]. Koilonychia is also seen with PPK progressiva (type Meleda) (Table 9.2); some other EDs (Tables 9.3, 9.4); monilethrix [147, 148], onychogryphosis [149]; the nail–patella syndrome (see "Nail–patella syndrome or hereditary osteoonychodysplasia"), incontinentia pigmenti (Table 9.7); trichoepithelioma multiplex [150] and in a syndrome with abnormally long eyelashes [151]. In trichomegaly koilonychia has otherwise not been reported [152].

Curved nail of the fourth toe (MIM 219070)

Plantarly curved nail deformity of the fourth toe with hypoplasia of the bone and soft tissue of the distal phalange was described by Iwasawa et al. [153]. Eight cases were reported by Higashi [154] without other anomalies of the extremities (see Chapter 2).

Overcurvature of the nails

Excessive transverse curvature of one or more nails may give the effect of an ingrowing toenail, often causing considerable discomfort [155, 156]. In hidrotic ED (Table 9.2) the nails are conical with distal ingrowing and increased convexity. They often fail to reach the end of the digit, appear small, and may have onycholysis and/or spontaneous shedding. Circumferential nails (see Table 9.11) also have an excessive curvature [157].

Ectopic nails, onychoheterotopia

(Figs 9.29–9.31)

After trauma to the nail matrix a portion of it can produce a nail outside the nail fold. A normal-appearing congenital ectopic nail on the palmar aspect of the thumb was described by Ohy and reported by Kikuchi et al. [158]. Kalisman and Kleinert [159] and Allieu et al. [160] reported a boy with circumferential nail growth over all sides of the small finger. Alves et al. [161] reported the same anomaly on a left ring finger. Congenital claw-like fingers and toes were seen in two siblings [162].

Ectopic calcaneal nail [163] has been reported in a patient whose sister, father, and father’s brother had the same lesion in the same location.

In a case reported by Kuniyuki [164] the right fifth finger and the left fourth finger presented with hard keratotic papules on the thin tip associated with a Y-shaped bifurcation on the distal phalanx of the former and an M-shaped depressed deformity in the phalanx of the latter.

Table 9.7 (Continued)

<table>
<thead>
<tr>
<th>Disease</th>
<th>Inheritance, gene, mapping</th>
<th>Comments</th>
</tr>
</thead>
<tbody>
<tr>
<td>Rubinstein–Taybi syndrome type 1 [677–682]</td>
<td>AD, CREBBP, 16p13.3 180849</td>
<td>Broad thumb and great toes. High palate, short stature, mental retardation; peculiar facies, keloid formation. Malalignment of the toenails</td>
</tr>
<tr>
<td>Rubinstein–Taybi syndrome type 2 [683, 684]</td>
<td>AD, EP300, 22q13.2 613684</td>
<td>Same phenotype but less severe than Rubinstein–Taybi type 1. Sometimes slightly broad thumbs, great toes, square distal fingerprints</td>
</tr>
<tr>
<td>Spieglers–Brooke syndrome and racket nails [685–688]</td>
<td>AD, CYLD, 16q12.1 605041</td>
<td>Brachydactyly. Turban tumors</td>
</tr>
<tr>
<td>Stub thumb with racket nail or brachydactyly type D [689, 690]</td>
<td>AD, HOXD13, 2q31.1 113200</td>
<td>No other defects</td>
</tr>
</tbody>
</table>

Inheritances are indicated as follows: AD, autosomal dominant; AR, autosomal recessive; XL, sex-linked transmission; XD, sex-linked dominant; XR, sex-linked recessive.
Ida et al. [165] reported a case of congenital ectopic nails on bilateral little fingers presenting as hyperkeratinized elevations on the tip of the palmar side below the nails and close to the free edge. Radiographs showed a depression on the tip of the distal phalanx.

A similar case was associated with Pierre Robin syndrome [166]. Circumferential toenails have also been described [157]. A fingernail and dorsal skin on the palmar surface with a normal nail on the dorsal surface was reported by Keret and Ger [167]. Two patients with congenital ectopic palmar nails of the little finger were associated with absent flexion in the finger [168]. In other reported cases the nails have been abnormally shaped [158, 164, 169–174]. They all appeared on the palmar or dorsal side 1 cm from the normal nail. Kinoshita et al. [175] reported a clam-like deformity of the little finger expressing the unusual appearance of the nail wrapping around the fingertip (probably close to the circumferential nail). Ectopic nails should be differentiated from rudimentary polydactyly [164, 176, 177]; from COIF [118]; and from the nail matrix doubling syndrome of Vigh and Pinter [130], characterized by thick nails, oculomotor paresis, debility, and aplasia of the external ear. A boy with a double nail on the right fifth finger and an ectopic nail on the left has also been described [178].
Congenital malformations caused by drugs or infections (see also Chapter 16)

Hydantoin (phenytoin) taken during pregnancy (MIM 132810) is known to cause malformations, including hypoplasia of nail and fingers, a broad short nose, ocular hypertelorism, ptosis, strabismus, and ear and mouth abnormalities [179]. Cleft lip, ventricular septum defects, and psychomotor retardation can also occur [180]. Trimethadione, paramethadione, and valproic acid can produce similar multiple defects [181, 182]. After valproic acid the nails were long and hyperconvex. After carbamazepine only hypoplastic nail changes were reported which normalized after some months [183]. After phenobarbital hypoplasia of nails and phalanges was observed [184]. Hyperpigmentation of several fingernails after hydantoin has also been described [185, 186]. It can be distal with detachment of the nail plate, diffuse, or occur as dark longitudinal streaks (Table 9.6).

Anticoagulant therapy with warfarin during the first trimester of pregnancy may give hypoplasia of nasal bones and the terminal phalanges together with stippled epiphyses: the fingernails are small and malformed. The syndrome has many features in common with the dominant type of chondrodysplasia punctata [187]. Malformations in infants of chronically alcoholic women are common and include growth deficiency, bone, eye, and cardiac anomalies, as well as hirsutism and nail hypoplasia [188]. Taylor et al. [189] reported koilonychia, transverse growth, hyperpigmentation, and thinning of nails in children born after maternal poisoning with polychlorinated biphenyls in rice oil.

Congenital cutaneous candidiasis is uncommon and can involve only the nails [190]. In congenital acquired immune deficiency syndrome (AIDS) the nails may appear yellow [191, 192].

Nail discoloration

Discoloration of nails is common. Abnormal color due to external factors staining the nail has been reviewed by Daniel [193] and the influence of drugs and systemic disorders has recently been discussed [194]. Leukonychias and their classification have been reviewed by Grossman and Scher [195]. The conditions associated with congenital and/or hereditary discoloration are listed in Table 9.8 according to color changes. Several of them are combined with other abnormalities and are therefore also mentioned elsewhere (see Chapter 2).

Epidermolysis bullosa (Figs 9.32–9.42)

The various forms of epidermolysis bullosa classified according to the recommendation of a 2014 consensus group [196] and their associated nail changes, which might aid in diagnosis, are listed in Table 9.9. The nail changes in epidermolysis bullosa have been reviewed by Bruckner-Tuderman et al. [197] and Tosti et al. [198].

Table 9.8 Conditions with congenital and/or hereditary discoloration of nails listed according to color changes.

<table>
<thead>
<tr>
<th>Disease</th>
<th>Color of the nail</th>
<th>Inheritance, gene, mapping</th>
<th>Comments</th>
</tr>
</thead>
<tbody>
<tr>
<td>Heimler syndrome type 1 [691, 692]</td>
<td>Partial leukonychia</td>
<td>AR, PEX1, 7q21.2 234580</td>
<td>Partial leukonychia and Beau’s line. Bilateral sensorineural hearing loss, enamel hypoplasia of permanent teeth</td>
</tr>
<tr>
<td>Heimler syndrome type 2 [692]</td>
<td>Leukonychia of fingernails</td>
<td>AR, PEX6, 6p21.1 616617</td>
<td>Slightly broad thumbs</td>
</tr>
<tr>
<td>Huriez syndrome or scleroatrophic and keratotic dermatosis of limbs [341, 693–695]</td>
<td>White</td>
<td>AD, 4q23 181600</td>
<td>Hypoplasia, longitudinal ridging, distal splitting, absent fingerprints</td>
</tr>
<tr>
<td>Keratitis, ichthyosis, and deafness (KID)</td>
<td>White, thick</td>
<td>AD, GJB2, 13q12.11 148210</td>
<td>See Table 9.2, KID syndrome</td>
</tr>
<tr>
<td>Leopard syndrome [696–700], LRPD1 (for PTPN11), LRPD2 (for RAF1), LRPD3 (for BRAF)</td>
<td>White with koilonychia</td>
<td>AD, PTPN11, RAF1, BRAF, 12q24.13, 3p25, 7q34 151100, 611554, 613707</td>
<td>Lentigines, electrocardiographic changes, hypertelorism, pulmonary stenosis, abnormalities of genitalia, retarded growth, deafness</td>
</tr>
<tr>
<td>Leukonychia totalis (sometimes reported as leukonychia subtotalis) [201, 701–706] or nail disorder non-syndromic congenital 3 (Table 9.1)</td>
<td>Milky or porcelain</td>
<td>AD, AR, PLC1, 3p22.2 151600</td>
<td>Pink areas (2–4 mm), distal to white area are described</td>
</tr>
<tr>
<td>Disease</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>--------</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Leukonychia totalis with epiphyseal dysplasia (Lowry–Wood) syndrome [707–709]</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Leukonychia totalis with PPK and congenital alopecia see also Table 9.2</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Leukonychia striata [710–712]</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Striated leukonychia with eruptive milia [713]</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Leukonychia with koilonychia [144, 145] or nail disorder non-syndromic congenital 2 (Table 9.1)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Leukonychia, koilonychia, deafness, knuckle pads, PPK [146, 257, 335]</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Leukonychia, multiple sebaceous cysts, renal calculi (steaocystoma multiplex) [94, 714, 715]</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Leukonychia, onychorrhexis, hypoparathyroidism, dental changes, cataract [716]</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Leukonychia, duodenal ulcer, and gallstones [717]</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Leukonychia with pili torti [718, 719]</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Leukonychia, axonal neuropathy, myopathic features, dilated cardiomyopathy, conduction disturbances and arrhythmia [720]</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Longitudinal pachyleukonychia [721]</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Acrokeratosis verruciformis</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Hope disease [722–725]</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Hemochromatosis [726–728]</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Hooft disease [729, 730]</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Familial amyloidosis with polyneuropathy [731–735]</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Disease</th>
<th>Color of the nail</th>
<th>Inheritance, gene, mapping</th>
<th>Comments</th>
</tr>
</thead>
<tbody>
<tr>
<td>Leukonychia totalis with epiphyseal dysplasia (Lowry–Wood) syndrome [707–709]</td>
<td>Milky</td>
<td>AR 226960</td>
<td>Also nystagmus, hypoplasia of corpus callosum, microcephaly</td>
</tr>
<tr>
<td>Leukonychia totalis with PPK and congenital alopecia see also Table 9.2</td>
<td>Milky dystrophic nail mild</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Leukonychia striata [710–712]</td>
<td>Milky or porcelain</td>
<td></td>
<td>Longitudinal or transverse band</td>
</tr>
<tr>
<td>Striated leukonychia with eruptive milia [713]</td>
<td>Milky or porcelain</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Leukonychia with koilonychia [144, 145] or nail disorder non-syndromic congenital 2 (Table 9.1)</td>
<td>Milky or porcelain</td>
<td></td>
<td>May be considered as a particular form of leukonychia totalis</td>
</tr>
<tr>
<td>Leukonychia, koilonychia, deafness, knuckle pads, PPK [146, 257, 335]</td>
<td>Milky or porcelain</td>
<td>AD, GBJ2, 13q12.11 149200</td>
<td></td>
</tr>
<tr>
<td>Leukonychia, multiple sebaceous cysts, renal calculi (steaocystoma multiplex) [94, 714, 715]</td>
<td>Milky or porcelain</td>
<td>AD, KRT17, 17q21.2 184500</td>
<td>Smith suggested that the disorder is sometimes a variant of PC-KRT17</td>
</tr>
<tr>
<td>Leukonychia, onychorrhexis, hypoparathyroidism, dental changes, cataract [716]</td>
<td>Milky or porcelain</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Leukonychia, duodenal ulcer, and gallstones [717]</td>
<td>Milky or porcelain</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Leukonychia with pili torti [718, 719]</td>
<td>White</td>
<td>AD</td>
<td>Leukonychia subtotalis is reported during childhood. Association with pseudoacanthosis nigricans is possible</td>
</tr>
<tr>
<td>Leukonychia, axonal neuropathy, myopathic features, dilated cardiomyopathy, conduction disturbances and arrhythmia [720]</td>
<td>White (total or partial)</td>
<td>AD, LMNA, 1q22</td>
<td></td>
</tr>
<tr>
<td>Longitudinal pachyleukonychia [721]</td>
<td>White</td>
<td>AD</td>
<td>Longitudinal white steaks 2.5–3.8 cm width. Exaggerated transverse curvature. Localized thickening. Epidermal hamartoma limited to the nail. No other dermatological features</td>
</tr>
<tr>
<td>Acrokeratosis verruciformis</td>
<td>White</td>
<td>AD, ATP2A2, 12q24.11</td>
<td>Verrucous or lichenoid papules on the dorsa of hands and fingers</td>
</tr>
<tr>
<td>Hope disease [722–725]</td>
<td>Brown</td>
<td>101900</td>
<td>Palms and soles may be involved as translucent punctae. Allelic to Darier disease in early years with ridging and subungual hyperkeratosis in later life</td>
</tr>
<tr>
<td>Hemochromatosis [726–728]</td>
<td>White, gray, or brownish</td>
<td>AR, HFE, BMP2, 6p22.2, 20p12.3 235200</td>
<td>Koilonychia in 50%. Periungual area brown</td>
</tr>
<tr>
<td>Hooft disease [729, 730]</td>
<td>Opaque leukonychia</td>
<td>AR 236300</td>
<td>Erythematosquamous eruption, tapetoretinal degeneration, low serum lipids</td>
</tr>
<tr>
<td>Familial amyloidosis with polyneuropathy [731–735]</td>
<td>Yellow</td>
<td>AD, LYZ, FGA, APOA1, B2M, 12q15, 4q31.3, 11q23, 15q21.1 105200</td>
<td>More marked on distal toenails</td>
</tr>
</tbody>
</table>

(Continued)
<table>
<thead>
<tr>
<th>Disease</th>
<th>Color of the nail</th>
<th>Inheritance, gene, mapping</th>
<th>Comments</th>
</tr>
</thead>
<tbody>
<tr>
<td>Incontinentia pigmenti</td>
<td>Slightly yellow</td>
<td>XD, IKBKG, Xq28 308300</td>
<td>See Table 9.5</td>
</tr>
<tr>
<td>Macular amyloidosis with familial nail dystrophy [736]</td>
<td>Yellow-brown</td>
<td>AD</td>
<td>Resolution of nail changes during third or fourth decade</td>
</tr>
<tr>
<td>Aplasia cutis with dystrophic nails [737]</td>
<td>Gray-yellow, brown periungual skin</td>
<td></td>
<td>Periungual skin</td>
</tr>
<tr>
<td>Pachyonychia congenita</td>
<td>Yellow or brown</td>
<td>AD, KRT16, KRT6A, 17q12-q21, 12q13 167200</td>
<td>See Table 9.2</td>
</tr>
<tr>
<td>Progeria</td>
<td>Yellow, atrophic</td>
<td>AD, LMNA, 1q22 176670</td>
<td>See Table 9.5</td>
</tr>
<tr>
<td>Yellow nail syndrome congenital [738, 739]</td>
<td>Yellow-green</td>
<td>AD, FOXC2 ?, 16q24.3 153300</td>
<td>Family history of lymphedema (see Table 9.11)</td>
</tr>
<tr>
<td>Acrodermatitis enteropathica [740, 741]</td>
<td>Brownish</td>
<td>AR, SLC39A4, 8q24.3 201100</td>
<td>FOXC2 gene is involved in lymphedema distichiasis with or without yellow nails</td>
</tr>
<tr>
<td>Acanthosis nigricans [742]</td>
<td>Gray-brown</td>
<td>AD</td>
<td></td>
</tr>
<tr>
<td>Darier–White disease [743–745]</td>
<td>Brown, red, or white</td>
<td>AD, ATP2A2, 12q23-q24 124200</td>
<td>Usually as longitudinal white and red streaks</td>
</tr>
<tr>
<td>Congenital phenytoin effect [185, 746]</td>
<td>Brown, red, and white</td>
<td>AD, EPHX1, 1q42.1 132810</td>
<td>Subungual, V-shaped keratoses</td>
</tr>
<tr>
<td>Congenital pigmented nevi of the nails [747, 748]</td>
<td>Brown, sometimes as longitudinal band</td>
<td></td>
<td>Nail/phalangeal hypoplasia</td>
</tr>
<tr>
<td>Ectodermal dysplasia syndromes</td>
<td>Dark, brown</td>
<td>AR, UROS, 10q25-q26 263700</td>
<td>Possible mutilation of hands and feet. Koilonychia</td>
</tr>
<tr>
<td>Congenital porphyria (Günther's) [751, 752]</td>
<td>Brown</td>
<td>AR, UROD, HFE, 1p34, 6p22.2 176100</td>
<td>Usually distal. Absence of lunula, early koilonychia</td>
</tr>
<tr>
<td>Porphyria cutanea tarda [753–755]</td>
<td>Yellow brown, Pigmentation in bands. Photoonycholysis</td>
<td>AD, UROD, HFE, 1p34, 6p22.2 176100</td>
<td></td>
</tr>
<tr>
<td>Angioma</td>
<td>Bluish-red nail bed</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>
Hereditary and Congenital Nail Disorders

<table>
<thead>
<tr>
<th>Disease</th>
<th>Color of the nail</th>
<th>Inheritance, gene, mapping</th>
<th>Comments</th>
</tr>
</thead>
<tbody>
<tr>
<td>Facioscapulohumoral muscular dystrophy. Coat’s disease might be associated [764, 765]</td>
<td>Bluish-red nail bed with telangiectasia</td>
<td>AD, contraction of D4Z4, 4q35 158900</td>
<td>Telangiectasias of face, conjunctiva, retina</td>
</tr>
<tr>
<td>Congenital heart disease [766]</td>
<td>Red-bluish lunula</td>
<td>AR, ATP7B, 13q14.3 277900</td>
<td>Deafness, muscles weakness. Mental retardation Clubbing</td>
</tr>
<tr>
<td>Hepatolenticular degeneration, Wilson disease [767, 768]</td>
<td>Azure lunula</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Hereditary benign telangiectasia [769–772]</td>
<td>Blue lunula and nail bed</td>
<td>AD, 5q14 187260</td>
<td>Blue lips and nipples, telangiectasia of chest, elbows, and dorsum of hands</td>
</tr>
<tr>
<td>Hereditary hemorrhagic telangiectasia (Rendu–Osler–Weber syndrome) [773–777]</td>
<td>Blue fine blood vessels</td>
<td>AD, ENG, 9q34.11 187300</td>
<td>Telangiectasia of face, conjunctiva, fingers, mucosa of nasopharynx and gastrointestinal tract</td>
</tr>
<tr>
<td>Telangiectasia hereditary hemorrhagic type 2 [778–780]</td>
<td>Blue fine blood vessels</td>
<td>AD, ACVRL1, 12q13.13 600376</td>
<td></td>
</tr>
<tr>
<td>Klippel–Trénaunay syndrome [781, 782]</td>
<td>Bluish</td>
<td>Isolated cases, PIK3CA, 3q26.32 149000</td>
<td>Large hemangioma with hypertrophy of bones and soft tissue</td>
</tr>
<tr>
<td>Nigremia. Hemoglobin M disease</td>
<td>Blue cyanotic</td>
<td>AD, alpha globin, 16p13.3 141800</td>
<td>Cyanosis of face. No clubbing. Brown hemoglobin M band on electrophoresis</td>
</tr>
<tr>
<td>Pernicious anemia [783–785]</td>
<td>Blue</td>
<td>AD 170900 AR, GIF, 11q12.1 261000</td>
<td>Hair changes</td>
</tr>
<tr>
<td>Peutz–Jeghers–Touraine syndrome [786]</td>
<td>Black</td>
<td>AD, STK11, 19p13.3 175200</td>
<td>Longitudinal bands; unusual clubbing (Table 9.6)</td>
</tr>
</tbody>
</table>

Inheritances are indicated as follows: AD, autosomal dominant; AR, autosomal recessive; XD, sex-linked dominant; ?, still unclear. PPK, palmoplantar keratoderma.

**Figure 9.32** Recessive dystrophic epidermolysis bullosa dystrophica, generalized intermediate. Twenty-four-year-old woman: some nails normal, some dystrophic, some absent.

**Figure 9.33** Recessive dystrophic epidermolysis bullosa, generalized severe. Forty-two-year-old man: severe nail dystrophy; mutilating epidermolysis bullosa with widespread blistering.
Various hereditary disorders with secondary nail changes appear in Table 9.10. In Table 9.11 disorders with non-classified nail involvement are listed. Nail abnormalities are reported in several severe conditions with in utero or very early lethality or complex chromosomal anomalies [199–203]. Elsewhere nail anomalies are not specific [204]. These conditions are not reported here.

Figure 9.34  Recessive dystrophic epidermolysis bullosa, generalized severe: nails of an 11-month-old girl. Courtesy of I. Anton-Lambrech.t.

Figure 9.35  Recessive dystrophic epidermolysis bullosa, generalized severe: 11-month-old boy with complete loss of nails. Courtesy of I. Anton-Lambrech.t.

Secondary nail changes and some miscellaneous nail conditions

Various hereditary disorders with secondary nail changes appear in Table 9.10. In Table 9.11 disorders with non-classified nail involvement are listed. Nail abnormalities are reported in several severe conditions with in utero or very early lethality or complex chromosomal anomalies [199–203]. Elsewhere nail anomalies are not specific [204]. These conditions are not reported here.

Figure 9.36  Dominant dystrophic epidermolysis bullosa, localized: 36-year-old man with nail dystrophy and blisters limited to the hands and feet. Courtesy of I. Anton-Lambrech.t.

Figure 9.37  Dominant dystrophic epidermolysis bullosa, generalized: 41-year-old man with thickened, short, and brittle nails. Courtesy of I. Anton-Lambrech.t.
Patients with tuberous sclerosis complex (TSC) have a mutation in a tumor suppressor gene: either TSC1 or TSC2. Tumor formation in multiple organs is accompanied by a somatic mutation that deactivates the wild-type allele, in accord with the two-hit hypothesis of Knudson. Tumors have been reported in the brain, heart, lungs, kidneys, and skin of patients with TSC. The skin tumors include facial angiofibromas, forehead plaques, shagreen patches, and ungual fibromas.

Ungual fibromas are a major diagnostic criterion for the diagnosis of TSC and a concern to patients because of pain and distortion of the nail. The most recent consensus criteria stipulated that ungual fibromas must be non-traumatic to serve as a major criterion, because single ungual fibromas occur in the general population in response to trauma.
<table>
<thead>
<tr>
<th>Subtype</th>
<th>Inheritance, gene, mapping</th>
<th>Nails</th>
<th>Comments</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Major type EB simplex</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Acral peeling skin syndrome</td>
<td>AR, TGM5, 15q15.2</td>
<td>Normal nails</td>
<td></td>
</tr>
<tr>
<td>EBS superficialis</td>
<td>AD</td>
<td>Normal</td>
<td></td>
</tr>
<tr>
<td>Acantholytic EBS</td>
<td>AR, DSP, 6p24, PKG 607600</td>
<td>Nail loss (frequency 100%)</td>
<td></td>
</tr>
<tr>
<td><strong>Skin fragility syndromes (SFS)</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>SFS with woolly hair</td>
<td>AR, DSP, 6p24 607655</td>
<td>Dystrophic or absent</td>
<td></td>
</tr>
<tr>
<td>SFS with ectodermal dysplasia</td>
<td>AR, PKP1, 1q32 604536</td>
<td>Thickened dystrophic nails (frequency 100%)</td>
<td></td>
</tr>
<tr>
<td>SFS plakoglobin deficiency</td>
<td>AR, JUP, 17q21.2</td>
<td>Dystrophic or absent</td>
<td></td>
</tr>
<tr>
<td>EBS localized</td>
<td>AD, KRT5, KRT14, 12q13, 17q12-q21 131800</td>
<td>Blistering may cause onycholysis and onychomadesis, with normal regrowth or thickened dystrophic nails (uncommon, 12% ?). Mostly normal</td>
<td>Previously called Weber–Cockayne</td>
</tr>
<tr>
<td>EBS generalized severe</td>
<td>AD, KRT5, KRT14, 12q13, 17q12-q21 131760</td>
<td>Onychomadesis, pachyonychia, onychogryphosis, pincer nails or absent nails (frequency &gt;75%). Loss with regeneration. End result dystrophic or normal</td>
<td>Includes patients previously with EBS Koebner</td>
</tr>
<tr>
<td>EBS generalized intermediate</td>
<td>AD, KRT5, KRT14, 12q13, 17q12-q21 131900</td>
<td>Onychomadesis, with normal regrowth, pachyonychia, thickened great toenail (frequency 14%)</td>
<td></td>
</tr>
<tr>
<td>EBS with mottled pigmentation</td>
<td>AD, KRT5, 13q13 131960</td>
<td>Peculiar curving, dystrophic nails, small toenail (frequency uncommon)</td>
<td>Pigmentation of the neck and the abdomen</td>
</tr>
<tr>
<td>EBS migratory circinate</td>
<td>AD, KRT5, 12q13 609352</td>
<td>Normal</td>
<td></td>
</tr>
<tr>
<td>EBS AR</td>
<td>AR, KRT14, KRT5 17q12-q21 601001</td>
<td>Hyperkeratotic nails, horizontal ridging, anonychia, mildly dystrophic toenails, micronychia of the fifth finger, and horizontal ridging consistent with onycomadesis of the other toenails</td>
<td></td>
</tr>
<tr>
<td><strong>Junctional EB</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>EBS with muscular dystrophy</td>
<td>AR, PLEC1, 8q24 226670</td>
<td>Onychomadesis, pachyonychia, onychogryphosis, pincer nails, anonychia (frequency 50%)</td>
<td></td>
</tr>
<tr>
<td>EBS with pyloric atresia</td>
<td>AR, PLEC1, ITGA6, ITGβ4, 8q24, 2q31.1, 17q11-qter 612138</td>
<td>Normal</td>
<td></td>
</tr>
<tr>
<td>EBS-Ogna</td>
<td>AD, PLEC1, 8q24 131950</td>
<td>Onychogryphosis of great toe in adulthood</td>
<td></td>
</tr>
<tr>
<td>EBS AR BP230 deficiency [787]</td>
<td>AR, DST, 6p12-p11 615425</td>
<td>Nail dystrophy of all toenails (particularly the great toes)</td>
<td></td>
</tr>
<tr>
<td>EBS AR exophilin deficiency</td>
<td>AR, EXPH5, 11q22.3 615028</td>
<td>Normal</td>
<td></td>
</tr>
</tbody>
</table>
### Table 9.9 (Continued)

<table>
<thead>
<tr>
<th>Subtype</th>
<th>Inheritance, gene, mapping</th>
<th>Nails</th>
<th>Comments</th>
</tr>
</thead>
<tbody>
<tr>
<td>EBS generalized, with scarring and hair loss</td>
<td>AD, KLHL24, 3q27 617294</td>
<td>Fragile and dystrophic toenails. Toenails thicken with age</td>
<td></td>
</tr>
<tr>
<td>JEB generalized severe</td>
<td>AR, LAMA3, LAMB3, LAMC2 18q11.2, 1q32, 1q25-q31 226700</td>
<td>Anonychia (frequency &gt;75%)</td>
<td></td>
</tr>
<tr>
<td>JEB generalized intermediate</td>
<td>AR, LAMA3, LAMB3, LAMC2 18q11.2, 1q32, 1q25-q31 226700</td>
<td>Pachyonychia, exuberant granulation, tissue nail erosion, anonychia (frequency &gt;75%)</td>
<td></td>
</tr>
<tr>
<td>JEB with pyloric atresia</td>
<td>AR, ITGA6, ITGβ4, 2q31.1, 17q11-pter 226650</td>
<td>Nail thinning and atrophy or absent nails</td>
<td></td>
</tr>
<tr>
<td>JEB late onset</td>
<td>AR, COL17A1, 10q24.3 10q24.3 226650</td>
<td>Onycholysis, nail loss, Beau's lines</td>
<td></td>
</tr>
<tr>
<td>JEB with respiratory and renal involvement, JEB localized</td>
<td>AR, ITGA3, 17q21 10q24.3 17q21 10q24.3 226650</td>
<td>Toenail dystrophy evident from 5 months</td>
<td></td>
</tr>
<tr>
<td>JEB inversa</td>
<td>AR, LAMA3, LAMB3, LAMC2 18q11.2, 1q32, 1q25-q31 226650</td>
<td>Dystrophic or absent nails (frequency &gt;50%)</td>
<td></td>
</tr>
<tr>
<td><strong>Dystrophic EB</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>JEB laryгоonychocutaneous syndrome</td>
<td>AR, LAMA3, 18q11.2 245660</td>
<td>Nail thickening, nail erosions with granulation tissue, anonychia (frequency 100%)</td>
<td></td>
</tr>
<tr>
<td>DDEB generalized</td>
<td>AD, COL7A1, 3p21.3 131750</td>
<td>Nail thickening, onychogryphosis, anonychia, pseudosyndactyly (frequency &gt;75%)</td>
<td></td>
</tr>
<tr>
<td>DDEB acral</td>
<td>AD/AR, COL7A1, 3p21.3 131750; 226600</td>
<td>Nail thickening, anonychia (frequency &gt;75%)</td>
<td></td>
</tr>
<tr>
<td>DDEB nails only</td>
<td>AD, COL7A1, 3p21.3 131750; 226600</td>
<td>Pachyonychia, thickened dystrophic nails, anonychia (frequency 100%)</td>
<td></td>
</tr>
<tr>
<td>DDEB and RDEB localized</td>
<td>AD, AR, COL7A1, 3p21.3 131750</td>
<td>Nail dystrophy or thickening</td>
<td></td>
</tr>
<tr>
<td>Pretibial DDEB or RDEB</td>
<td>AD/AR, COL7A1, 3p21.3 131850; 226600</td>
<td>Nail thickening (frequency &gt;75%), short</td>
<td></td>
</tr>
</tbody>
</table>

*(Continued)*
Table 9.9 (Continued)

<table>
<thead>
<tr>
<th>Subtype</th>
<th>Inheritance, gene, mapping</th>
<th>Nails</th>
<th>Comments</th>
</tr>
</thead>
<tbody>
<tr>
<td>Pruriginous DDEB or RDEB</td>
<td>AD/AR, COL7A1, 3p21.3</td>
<td>Nail thickening, anonychia (frequency &gt;75%)</td>
<td></td>
</tr>
<tr>
<td></td>
<td>604129</td>
<td></td>
<td></td>
</tr>
<tr>
<td>DEB–bullous dermolysis of the newborn</td>
<td>AD/AR, COL7A1, 3p21.3</td>
<td>Nail thickening, anonychia, pseudosyndactyly (frequency 25–50%)</td>
<td></td>
</tr>
<tr>
<td></td>
<td>131705</td>
<td></td>
<td></td>
</tr>
<tr>
<td>RDEB generalized severe</td>
<td>AR, COL7A1, 3p21.3</td>
<td>Anonychia, pseudosyndactyly (frequency &gt;75%)</td>
<td></td>
</tr>
<tr>
<td></td>
<td>226600</td>
<td></td>
<td></td>
</tr>
<tr>
<td>RDEB generalized intermediate</td>
<td>AR, COL7A1, 3p21.3</td>
<td>Dystrophic or absent nails (frequency &gt;75%)</td>
<td></td>
</tr>
<tr>
<td></td>
<td>226600</td>
<td></td>
<td></td>
</tr>
<tr>
<td>RDEB inversa</td>
<td>AR, COL7A1, 3p21.3</td>
<td>Nail thickening (frequency &gt;75%)</td>
<td></td>
</tr>
<tr>
<td></td>
<td>226600</td>
<td></td>
<td></td>
</tr>
<tr>
<td>RDEB centripetalis</td>
<td>AR, COL7A1, 3p21.3</td>
<td>Dystrophic or absent nails (frequency &gt;75%)</td>
<td></td>
</tr>
<tr>
<td></td>
<td>226600</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Kindler syndrome</td>
<td>AR, KIND‐1, 20p13</td>
<td>Nail dystrophy, parrot beak nail deformity, absent nails (Table 9.2)</td>
<td></td>
</tr>
<tr>
<td></td>
<td>173650</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Inheritances are indicated as follows: AD, autosomal dominant; AR, autosomal recessive.

DDEB, dominant dystrophic epidermolysis bullosa; EBS, epidermolysis bullosa simplex; JEB; junctional epidermolysis bullosa; RDEB, recessive dystrophic epidermolysis bullosa.

Table 9.10 Hereditary disorders with secondary nail changes.

<table>
<thead>
<tr>
<th>Disease</th>
<th>Inheritance, MIM</th>
<th>Nails</th>
<th>Comments</th>
</tr>
</thead>
<tbody>
<tr>
<td>Acanthosis nigricans (benign hereditary) [788]</td>
<td>AD 100600</td>
<td>Thick, friable, dull, gray, or normal</td>
<td>Pigmented, thick skin on neck, axilla, and inguinal region (Table 9.8)</td>
</tr>
<tr>
<td>Acrodermatitis enteropathica</td>
<td>AR, SL.C39A4, 8q24.3 201100</td>
<td>Periungual eczema, Candida infection. Multiple Beau’s lines</td>
<td>Alopecia, typical acral skin lesion, enteropathia (Table 9.8)</td>
</tr>
<tr>
<td>Aminogenic alopecia deficiency [789]</td>
<td>AR</td>
<td>Brittle</td>
<td>Argininosuccinic aciduria. Loss of hair</td>
</tr>
<tr>
<td>Citrullinemia, classic [790, 791]</td>
<td>AR, ASS1, 9q34.11 215700</td>
<td>Clubbed. Red transverse band distally</td>
<td>Trichorrhexis. Cutaneous atrophy</td>
</tr>
<tr>
<td>Congenital insensitivity to pain [792–794]</td>
<td>AR, NTRK1, 1q23.1 256800</td>
<td>Brittle</td>
<td>Hyperammonemia</td>
</tr>
<tr>
<td>Diabetes</td>
<td>AD, AR several susceptibility loci</td>
<td>Candida infection. Thick nails on fingers and toes</td>
<td>Argininosuccinic synthetase deficiency Anhidrosis. Mental retardation –</td>
</tr>
<tr>
<td>Gingival fibromatosis [29, 795–797]</td>
<td>AD, KCNH1, 1q32.2 135500</td>
<td>Small or absent nails of thumb and great toe</td>
<td>Gingival fibroma. Big nose and ears. Hepatosplenomegaly. Distal phalanges short Sometimes hypertrichosis, mental retardation, or ocular changes</td>
</tr>
<tr>
<td>Disease</td>
<td>Inheritance, MIM</td>
<td>Nails</td>
<td>Comments</td>
</tr>
<tr>
<td>---------</td>
<td>-----------------</td>
<td>-------</td>
<td>----------</td>
</tr>
<tr>
<td>Hyper-IgE syndrome [798–802]</td>
<td>AD, STAT3, 17q21.2</td>
<td>Hyperkeratotic or atrophic nails due to <em>Candida</em> infections. Mild clubbing</td>
<td>Defect in polymorphonuclear neutrophil function. Red scaly skin lesions. Cold staphylococcal abscess</td>
</tr>
<tr>
<td></td>
<td>147060</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>AR, DOCK8, 9p24</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>243700</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Hyperuricemia [803]</td>
<td>AD</td>
<td>Thick, split, dystrophic</td>
<td>Mental retardation</td>
</tr>
<tr>
<td>Interferonopathies (type 1) [804]</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Aicardi–Goutières syndrome Type 1</td>
<td>AD, AR, TREX1, 3p21</td>
<td>Dystrophic, erythematous periungual skin</td>
<td>Encephalopathy, basal ganglia calcifications, elevated interferon-alpha in blood and cerebral spinal fluid</td>
</tr>
<tr>
<td>Type 2</td>
<td>AR, RNASEH2B, 13q14</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>610181</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Type 3</td>
<td>AR, RNASEH2C, 11q13</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>610330</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Type 4</td>
<td>AR, RNASEH2A, 19p13</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>610333</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Type 5</td>
<td>AR, SAMHD1, 20q11</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>612952</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Type 6</td>
<td>AD, AR, ADAR1, 1q21</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>615010</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Type 7</td>
<td>AD, IFIH1, 2q24</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>615846</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Familial chilblain lupus</td>
<td></td>
<td>Subungual lesions (in some patients)</td>
<td>Painful Bluish-red papular or nodular lesions of the skin in acral locations (including the dorsal aspects of fingers and toes, heels, nose, cheeks, ears, and, in some cases, knees) precipitated by cold and wet exposure</td>
</tr>
<tr>
<td>Type 1</td>
<td>AD, TREX1, 3p21</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>610448</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Type 2</td>
<td>AD, SAMHD1, 20q11</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>614415</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>AD, TMEM173, 5q31</td>
<td></td>
<td></td>
</tr>
<tr>
<td>PRAAS (CANDLE) Proteasome-associated autoimmune inflammatory syndromes pseudo-TORCH syndrome type 2</td>
<td>AR, PSMB8, 6p21</td>
<td>Not described</td>
<td>Joint contractures, muscular atrophy, microcytic anemia, and panniculitis-induced lipodystrophy</td>
</tr>
<tr>
<td></td>
<td>256040</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>AR, PSMB4, 1q21</td>
<td>Not described</td>
<td>Antenatal onset of intracranial hemorrhage, calcification, brain malformations, liver dysfunction, and often thrombocytopenia</td>
</tr>
<tr>
<td></td>
<td>AR, USP18, 22q11.21</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>617397</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Reticulate pigmented disorder with systemic manifestations</td>
<td>XL, POLA1, Xp22.1-p21.3</td>
<td>Nail clubbing</td>
<td>Brown pigmentation of the skin following lines of Blaschko (females) or reticulate (males). Severe gastrointestinal disorders in infancy with failure to thrive and early death (males). Corneal dystrophy, severe photophobia, or chronic respiratory disease (males)</td>
</tr>
<tr>
<td></td>
<td>301220</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Disease</td>
<td>Inheritance, MIM</td>
<td>Nails</td>
<td>Comments</td>
</tr>
<tr>
<td>---------</td>
<td>----------------</td>
<td>-------</td>
<td>----------</td>
</tr>
<tr>
<td>Singleton–Merten syndrome</td>
<td>Type 1 AD, IFIH1, 2q24 182250</td>
<td>Onycholysis, subungual calcifications (in some patients)</td>
<td>Abnormalities of blood vessels, teeth, and bone. Calcifications of the aorta and aortic and mitral valves occur in childhood or puberty and can lead to early death</td>
</tr>
<tr>
<td></td>
<td>Type 2 (atypical) AD, RIG-1 (DDX58), 9p21 616298</td>
<td>Not described</td>
<td>Glaucoma, aortic calcification, and skeletal abnormalities, without dental anomalies</td>
</tr>
<tr>
<td>SPENCD (spondyloenchodrodysplasia with immune dysregulation)</td>
<td>AR, ACP5, 19p13.2 607944</td>
<td>Not described</td>
<td>Neurological involvement, radiolucent and irregular spondylar and metaphyseal lesions</td>
</tr>
<tr>
<td>Sting-associated vasculopathy with onset in infancy (SAVI)</td>
<td>AD, TMEM173, 5q31 612374</td>
<td>Nail fold capillary tortuosity, nail dystrophy, or nail loss</td>
<td>Recurrent respiratory infections, Raynaud phenomenon, rash, ulcerations, and amputations of extremities, nose, and ears</td>
</tr>
<tr>
<td>Systemic lupus erythematosus (152700)</td>
<td>AD, TREX1, 3p21</td>
<td>Pincer nail, onycholysis, and longitudinal ridging</td>
<td>Erythematous malar rash, photosensitivity</td>
</tr>
<tr>
<td>Trichohepatoenteric syndrome type 2</td>
<td>AR, SKIV2L, 6p21 614602</td>
<td>Not described</td>
<td>Intraterine growth retardation, facial dysmorphism, hair abnormalities, intractable diarrhea, and immunodeficiency</td>
</tr>
<tr>
<td>Lesh–Nyhan syndrome [805, 806]</td>
<td>XL, HPRT1, Xq26.2-q26.3 300322</td>
<td>Destroyed</td>
<td>Self-mutilation</td>
</tr>
<tr>
<td>Lichen planus familial [807–810]</td>
<td>AD 151620</td>
<td>Destroyed</td>
<td>Microchimerism is reported</td>
</tr>
<tr>
<td>Lymphedema with yellow nails [811] and mental retardation [740]</td>
<td>AD 153300</td>
<td>Thick yellow nails</td>
<td>Congenital lymphedema with adult onset and respiratory tract infection (Table 9.8)</td>
</tr>
<tr>
<td>Multiple cartilaginous exostosis Diaphyseal aclasis [812–818]</td>
<td>AD, EXT1, 8q24.11 133700</td>
<td>Non-tender nodules of proximal part of nail fold with elevation and splitting of nail</td>
<td>Retardation of growth of long bones and sarcomatous degeneration reported</td>
</tr>
<tr>
<td></td>
<td>AD, EXT2, 11p11.2 133701</td>
<td></td>
<td>A third locus on 19p is suspected</td>
</tr>
<tr>
<td>Neurofibromatosis type 1 (Recklinghausen) [819–821]</td>
<td>AD, NFI, 17q11.2 162200</td>
<td>One or more hypertrophic fingers or toes with dislocation of nails. Subungual glomus tumors are reported</td>
<td>Multiple neurofibromas, cutaneous pigmentation, central nervous involvement</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Thick, ridged, or fissured, pterygium</td>
<td></td>
</tr>
<tr>
<td>Porokeratosis multiple types (POROK1, –3, –6, –7, and -9)</td>
<td></td>
<td></td>
<td>Centrifugal spreading patches with central atrophy</td>
</tr>
<tr>
<td></td>
<td>Palmoplantar and disseminated (POROK2)</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>Disseminated superficial actinic (POROK4, 5 and 8) [822, 823]</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>POROK1 (175800)</td>
<td>AD, PMVK, 1q21.3</td>
<td></td>
</tr>
<tr>
<td></td>
<td>POROK2 (175850)</td>
<td>AD, 12q24.1-q24.2</td>
<td></td>
</tr>
<tr>
<td></td>
<td>POROK3 (175900)</td>
<td>AD, MVK, 12q24.11</td>
<td></td>
</tr>
<tr>
<td></td>
<td>POROK4 (607728)</td>
<td>15q25-q26.1</td>
<td></td>
</tr>
</tbody>
</table>
### Table 9.10 (Continued)

<table>
<thead>
<tr>
<th>Disease</th>
<th>Inheritance, MIM</th>
<th>Nails</th>
<th>Comments</th>
</tr>
</thead>
<tbody>
<tr>
<td>Acrorenal ocular syndrome [828] probably part of papillorenal syndrome (MIM 120330)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Ainhum, amniotic constriction band [829]</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Circumferential, curved fingernail. Congenital claw-like fingers and toes [156, 163, 165, 830]</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Congenital hereditary endothelial dystrophy with nail hypoplasia, previously CHED2 [831–833]</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Congenital ingrown toenails resulting in malalignment of the great toenail [834–841]</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Congenital subungual pterygium [842–848]</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Dysplasia of the fifth toenail [849]</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Epidermodysplasia verruciformis-like dermatoses with nail changes [850]</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Inheritances are indicated as follows: AD, autosomal dominant; AR, autosomal recessive; XD, sex-linked dominant; XL sex-linked recessive. IgE, immunoglobulin E; PRAAS, proteasome-associated autoinflammatory syndrome.

### Table 9.11 Various hereditary, familial or congenital disorders with nail involvement.

<table>
<thead>
<tr>
<th>Disease</th>
<th>Nails</th>
<th>Inheritance, gene, mapping, MIM</th>
<th>Comments</th>
</tr>
</thead>
<tbody>
<tr>
<td>Acrorenal ocular syndrome [828] probably part of papillorenal syndrome (MIM 120330)</td>
<td></td>
<td></td>
<td>Renal and ocular anomalies. Ptosis</td>
</tr>
<tr>
<td>Ainhum, amniotic constriction band [829]</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Circumferential, curved fingernail. Congenital claw-like fingers and toes [156, 163, 165, 830]</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Congenital hereditary endothelial dystrophy with nail hypoplasia, previously CHED2 [831–833]</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Congenital ingrown toenails resulting in malalignment of the great toenail [834–841]</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Congenital subungual pterygium [842–848]</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Dysplasia of the fifth toenail [849]</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Epidermodysplasia verruciformis-like dermatoses with nail changes [850]</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

(Continued)
<table>
<thead>
<tr>
<th>Disease</th>
<th>Nails</th>
<th>Inheritance, gene, mapping, MIM</th>
<th>Comments</th>
</tr>
</thead>
<tbody>
<tr>
<td>Familial nail dysplasia [851, 852], might be part of NDNC-7 (MIM 605779) or NDNC-10 (614157) see Table 9.1</td>
<td>Dysplastic nails affecting all nails</td>
<td>AD, FZD6, 8q22, 17p13</td>
<td></td>
</tr>
<tr>
<td>Familial twenty-nail dystrophy [853, 854] NDNC-1</td>
<td>Longitudinal ridging, rough, loss of luster</td>
<td>AD 161050</td>
<td>Trachonychia can also be acquired</td>
</tr>
<tr>
<td>Great toenail dysplasia [855]</td>
<td>Affected nails, dystrophic and brownish</td>
<td>–</td>
<td>See congenital malalignment of great toenail.</td>
</tr>
<tr>
<td>Hypocalcified enamel and dystrophic nails [856]</td>
<td>Dysplastic, striated on fingers and toes</td>
<td>XR</td>
<td>Hypoplastic enamel on permanent teeth. Patients otherwise normal</td>
</tr>
<tr>
<td>Idiopathic familial onychomadesis [857]</td>
<td>Recurrent onychomadesis</td>
<td></td>
<td>Multiple digits. Absence of any causal disease and medication</td>
</tr>
<tr>
<td>Inherited toenail dysplasia [858]</td>
<td>Said to be identical to Samman’s dystrophy</td>
<td>AD</td>
<td>Spontaneous resolution can occur</td>
</tr>
<tr>
<td>Kabuki syndrome type 1 [859]</td>
<td>Hypoplastic fingernails</td>
<td>AD, KMT2D, 12q13.12 147920</td>
<td>Congenital mental retardation, postnatal dwarfism, a peculiar facies reminiscent of the make-up of actors of Kabuki (Japanese traditional theatrical form), scoliosis, short fifth finger, persistence of fingerpads, radiographic abnormalities of the vertebrae, hands, and hip joints, and recurrent otitis media in infancy</td>
</tr>
<tr>
<td>Kenny–Caffey syndrome type 2 [860]</td>
<td>Dysplastic triangular finger and toenails</td>
<td>AD, FAM111A, 11q12.1 127000</td>
<td>Proportionate short stature, cortical thickening, and medullary stenosis of the tubular bones, delayed closure of anterior fontanel, eye abnormalities, and transient hypocalcemia.</td>
</tr>
<tr>
<td>Hand–foot–genital syndrome [861]</td>
<td>Small or absent nails (may involve all nails)</td>
<td>AD, HOXA13, 7p15.2 140000 176305</td>
<td>Short thumbs and occasionally proximally placed thumbs with short first metacarpals and small thenar eminences, short middle phalanges of hypoplasias, longitudinal vaginal septum, bifid uterus, vesicoureteral reflux, and ureteropelvic junction obstruction</td>
</tr>
<tr>
<td>Allelic to Guttmacher syndrome (more severe)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Leprechaunism or Donohue syndrome [862]</td>
<td>Hyperconvex</td>
<td>AR, INSR, 19p13.2 246200</td>
<td>Wrinkled loose skin. Decreased subcutaneous fat.</td>
</tr>
<tr>
<td>Mabry syndrome or hyperphosphatasia with mental retardation syndrome 1</td>
<td>Hypoplastic, fragile, or curved nails</td>
<td>AR, PIGV, 1p36.11 PIgL, 17p11.2, 239300</td>
<td>Mental retardation, seizures and hypotonia, and hyperphosphatemia</td>
</tr>
<tr>
<td>(HPRMS1) [863]</td>
<td></td>
<td></td>
<td>Facial dysmorphism and variable degrees of brachytelephalangy</td>
</tr>
<tr>
<td>Macular amyloidosis with familial nail dystrophy [736]</td>
<td>See Table 9.7</td>
<td>–</td>
<td>–</td>
</tr>
</tbody>
</table>

Table 9.11 (Continued)
### Table 9.11 (Continued)

<table>
<thead>
<tr>
<th>Disease</th>
<th>Nails</th>
<th>Inheritance, gene, mapping, MIM</th>
<th>Comments</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mammary–digital–nail syndrome [864]</td>
<td>Onychodystrophy, anonychia</td>
<td>AD, 22q12.3q13.1 61689</td>
<td>Juvenile hypertrophy of breasts in females. Hypoplasia or absence of distal phalanges</td>
</tr>
<tr>
<td>Multiple congenital anomalies–hypotonia–seizures syndrome [865]</td>
<td>Undeveloped nails, hypoplastic nails</td>
<td>AR, PIGN, 18q21 614080</td>
<td>Neonatal hypoponita, lack of psychomotor development, seizures, dysmorphic features, and variable congenital anomalies involving the cardiac, urinary, and gastrointestinal systems</td>
</tr>
<tr>
<td>Myhre syndrome [866]</td>
<td>Hyperconvex nails</td>
<td>AD, SMAD4, 18q21 139210</td>
<td>Growth–mental deficiency, laryngotracheal stenosis, arthropathy, prognathism, and short stature, pericarditis</td>
</tr>
<tr>
<td>Osteopoikilosis; Buschke–Ollendorff syndrome [867]</td>
<td>Pitting and “oil” spots. Onycholysis</td>
<td>AD, LEMD3, 12q14.3 166700</td>
<td>Dermatofibrosis lenticularis yellow papular arms and legs. Radiological features typical</td>
</tr>
<tr>
<td>Phelan–McDermid syndrome</td>
<td>Dysplastic toenails</td>
<td>Isolated cases, deletion of chromosome 22q13.3 606232</td>
<td>Neonatal hypopontia, global developmental delay, normal to accelerated growth, absent to severely delayed speech, autistic behavior</td>
</tr>
<tr>
<td>Pineal hyperplasia, insulin-resistant diabetes mellitus, and somatic abnormalities [868]</td>
<td>Onychauxis</td>
<td>AR, INSR, 19p13.2 262190</td>
<td>Short stature, acanthosis nigricans, precocious puberty</td>
</tr>
<tr>
<td>Pili torti syndrome [869]</td>
<td>Onychodysplasia</td>
<td>AD</td>
<td>Appears after puberty. See also pili torti (Table 9.4)</td>
</tr>
<tr>
<td>Rud syndrome [870]</td>
<td>Increased lunula on hands</td>
<td>XL (contiguous gene syndrome) 308200</td>
<td>Congenital ichthyosis and male hypogonadism, epilepsy, mental retardation, retinitis pigmentosa</td>
</tr>
<tr>
<td>Schinzel–Giedion syndrome, midface retraction syndrome [871, 872]</td>
<td>Hyperconvex nails</td>
<td>AR, SETBP1, 18q21 269150</td>
<td>Severe mental retardation, severe midface retraction, multiple skeletal anomalies, susceptibility to neuroepithelial neoplasia</td>
</tr>
<tr>
<td>Soft nail disease [873] may be part of NDNC-2 (Table 9.1)</td>
<td>Atrophic short soft nail. Absence of lunula</td>
<td>–</td>
<td>A single case</td>
</tr>
<tr>
<td>SOFT syndrome (short stature, onychodysplasia, facial dysmorphism, and hypotrichosis) [874]</td>
<td>Hypoplastic nails</td>
<td>AR, POC1A, 3p21.2 614813</td>
<td>Short stature, disproportionate, prenatal onset. Triangular face, short thickened distal phalanx</td>
</tr>
<tr>
<td>Trichoepithelioma multiple familial type 2 [153, 875]</td>
<td>Dystrophic nail, thumb nails most affected</td>
<td>AD, 9p21, CYLD 601606</td>
<td>Only dystrophic nails in some</td>
</tr>
<tr>
<td>Trichomegaly syndrome [828, 876]</td>
<td>Koilonychia</td>
<td>AR, FGF5, 4q21.21 190330</td>
<td>Abnormally long eyelashes. Sparse scalp hair, eye disorders, and mental retardation can occur</td>
</tr>
<tr>
<td>T-cell immunodeficiency, congenital alopecia and nail dystrophy [877]</td>
<td>Ridging and pitting of all nails</td>
<td>AR, FOXX1, 17q11.2 601705</td>
<td>Immunodeficiency</td>
</tr>
</tbody>
</table>

Inheritances are indicated as follows: AD, autosomal dominant; AR, autosomal recessive; XL, sex-linked transmission; XD, sex-linked dominant; XR, sex-linked recessive; ?, still unclear.
The frequency of ungual fibromas varies in studies from 15% to 52%. Ungual fibromas are among the last skin lesions to appear in TSC, with onset typically in the second decade and as late as the fifth decade. About half of the patients with ungual fibromas have both periungual and subungual lesions, with periungual fibromas predominating overall. Periungual fibromas are pink papules originating from under the proximal or lateral nail fold. Their shapes resemble garlic cloves, or are globoid, fusiform, or vermiform. Most have a hyperkeratotic tip, sometimes with punctated hemorrhage just proximal to the tip. The underlying nail plate has a longitudinal groove that usually approximates the width of the fibroma. Nails distorted by multiple large periungual fibromas are dystrophic or absent. Longitudinal nail grooves are also observed in the absence of any visible periungual fibroma. Nails of some patients have multiple longitudinal striations. Subungual fibromas are observed as pink papules originating under the nail plate. Those located more distally protrude from beneath the nail plate as focal areas of hyperkeratosis or larger papules. More proximal or larger fibromas lift the nail plate and are accompanied by subungual hyperkeratosis. Small subungual fibromas do not protrude, but are visible under the nail as oval, red, or white discolorations.

In addition to these classic TSC findings, some patients have subungual red comets, splinter hemorrhages, and longitudinal leukonychia. Red comets are partially blanchable longitudinal streaks that have a larger distal head with a narrowing proximal tail. They are solitary or multiple and made more evident with light pressure applied to the nail. Some comets have a whitish halo around the distal portion of the comet. Most patients are unaware of their presence. Comets are frequently associated with splinter hemorrhages, within and distal to the comet. Longitudinal leukonychia appears as white streaks extending from the nail matrix to the end of the nail.

Toenails have significantly more periungual fibromas than fingernails. Subungual fibromas and comets show the opposite distribution, with significantly more subungual fibromas and comets on fingernails than toenails. Periungual fibromas are most common on the fifth toe and subungual fibromas on the central third of the thumb.

MOSAIC DISORDERS INVOLVING THE NAIL REGION

Rudolf Happle

Introduction

Mosaic disorders can most easily be studied in the skin and therefore may involve the nail apparatus. Three groups of mosaic nail disorders can be distinguished in the form of ungual hamartomas, diseases reflecting functional X-chromosome mosaicism, and some particular linear inflammatory skin disorders involving the nail region.

Hamartomas

All hamartomas reflect mosaicism [208]. They are benign tumors composed of abnormally distributed tissue that may or may not show proliferative growth [209, 210]. Most of the following hamartomatous lesions interfere with nail growth on rare occasions only, whereas some few of them do this rather frequently.

Periungual fibromas of tuberous sclerosis

Periungual fibromas are a highly characteristic feature of tuberous sclerosis (see Chapter 21). Sometimes such tumors occur without any other sign of tuberous sclerosis. When they involve several digits [211, 212], a diagnosis of monosymptomatic tuberous sclerosis is easily made. Mashhood and Amjad [213] described a young man with type 1 segmental mosaicism of tuberous sclerosis [214]. He had cutaneous and ocular features that involved exclusively the right side of his body, including ipsilateral periungual fibromas of fingers and toes.

Acral keratotic lesions of PTEN hamartoma syndrome

PTEN hamartoma syndrome occurs in two different variants [215]. The Cowden variant is predominantly noted in females, whereas the Bannayan–Riley–Ruvalcaba variant occurs predominantly in males. The characteristic cutaneous features of the Cowden variant are multiple trichilemmomas, sclerotic fibromas, oral papillomas, and acral keratotic papules (Fig. 9.43). The acral lesions may also involve the nail organ, forming subungual keratotic hamartomas.

Storiform collagenoma

A solitary subungual storiform collagenoma was described in a patient without any features of PTEN hamartoma syndrome [216].

Nevus sebaceus

When the linear lesions of a systematized nevus sebaceus reach the nail organ, the nail plates may be covered with scurf [217].

Neurofibroma

A subungual neurofibroma has been documented in several reports [218, 219]. Remarkably, however, all of these reports described a solitary lesion. Hence, the question of whether these tumors belong to the clinical spectrum of neurofibromatosis 1 cannot be answered as yet.
Hereditary and Congenital Nail Disorders

Glomus tumor

The subungual glomus tumors are rather painful lesions (see Chapter 21). It is important to realize that these vascular hamartomas do not belong to the spectrum of hereditary glomangiomas (alias “glomuvenous malformations”), but represent a distinct entity. The OMIM entry 138000 is misleading because it conflates the two disorders.

Glomus tumors as a feature of neurofibromatosis 1

Remarkably, subungual glomus tumors belong to the clinical spectrum of neurofibromatosis 1 [220, 221]. Sometimes, several fingers are involved [221, 222].

Melanocytic nevus

In addition to the well-known melanocytic nevi of the nail matrix or bed, intradermal lesions may involve the proximal nail fold [223].

Onychomatricoma

Onychomatricoma is described elsewhere (see Chapter 21).

Eccrine angiomatous hamartoma

A 37-year-old woman had multiple eccrine angiomatous hamartomas involving the digits of her left hand and right foot, resulting in nail destruction (Fig. 9.44) [224]. The mosaic arrangement of lesions strongly suggests that the disorder was caused by a postzygotic mutation within the unknown gene.

Nail disorders reflecting functional X-chromosome mosaicism

In women affected with X-linked skin disorders, a mosaic involvement of nails may be noted as a result of X-inactivation (lyonization). Many of these phenotypes are caused by X-linked, male-lethal mutations.

CHILD nevus

The CHILD nevus represents a hallmark of CHILD syndrome (congenital hemidyssplasia with ichthyosiform nevus and limb defects) [225], which is inherited as an X-linked, male-lethal trait. The disorder tends to show a strikingly unilateral arrangement of lesions, but a mild contralateral involvement may also be noted. When the inflammatory lesions reach the nail region, they may cause ungual dystrophy or hyperplasia (Fig. 9.45a). A progressive thickening of the nail plate may even mimic pachyonychia congenita (Fig. 9.45b). Sometimes, the distal phalanx may be covered by a strawberry-like tumor that is pathognomonic of CHILD syndrome (Fig. 9.46a). It represents a verruciform xanthoma that develops from the proximal nail fold, with minimal or even absent damage of the nail plate (Fig. 9.46b). This conspicuous lesion was first documented by Otto Sachs in 1903 (Fig. 9.47) [226, 227]. On rare occasions, even several fingers may be involved.
Figure 9.45 CHILD (congenital hemidysplasia with ichthyosiform nevus and limb defects) nevus affecting the nails. (a) Lateralized ungual dystrophy in a 3-year-old girl. Note the mild involvement of the contralateral median digit. (b) The same girl at 11 years of age with hyperplastic nail plates reminiscent of pachyonychia congenita.

Figure 9.46 Pathognomonic strawberry-like acral hamartoma, originating from the proximal nail fold in a young girl with CHILD (congenital hemidysplasia with ichthyosiform nevus and limb defects) syndrome. (a) Before treatment. (b) Postoperative state. The defect was covered with a full-thickness skin graft. Note mild damage to the nail plate that remained untreated.
Conradi–Hünermann–Happle syndrome
Malformation of nails has sometimes been reported [228–230]. Characteristic features are platonychia and onychoschizia [231].

Incontinentia pigmenti
The nails of adult patients may show dystrophy of an entire nail or part of it. It is important to realize that in some adult women painful onychodystrophy of some fingers may constitute the only major complaint (Fig. 9.48), whereas other features such as small bald patches on the scalp or linear atrophy of the calves may go unnoticed [232]. Nicolau and Graham-Brown described a 57-year-old woman who was born in 1945. In 1956 she presented nail dystrophy and was initially treated with oral arsenic for non-existent nail psoriasis. In 1958 she received X-ray therapy of the nails. In 1977 she gave birth to a daughter with incontinentia pigmenti. Nevertheless, she received oral antifungal treatment for non-existent ungual tinea from 1980 until 1990. Finally, a molecular analysis performed in 2002 revealed a classical NEMO deletion in both mother and daughter [233]. Moreover, painful subungual tumors may represent a major complaint of adult women affected with incontinentia pigmenti [234, 235].

Focal dermal hypoplasia
Affected women may show longitudinal ridging or splitting of nail plates, micronychia, or V-shaped notches in the distal free margins of nail plates (Fig. 9.49) [236].

Börjeson–Forssman–Lehmann syndrome
This rather complex X-linked disorder is caused by PHF6 mutations. It was initially described in males who had mental deficiency, seizures, endocrine disturbances with gynecomastia, deep-set eyes, large ears, and brachyphalangy [237]. Paradoxically, female carriers show a rather peculiar phenotype. On their hands and feet, characteristic signs are tapering of fingers, syndactyly, brachyclinodactyly, and hypoplastic or dysplastic nails in an asymmetrical arrangement reflecting lyonization (Fig. 9.50a–c) [238].
Other mosaic disorders involving the nail region

Several other mosaic skin disorders may involve the nail region.

Inflammatory linear verrucous epidermal nevus (ILVEN)

This disorder represents a dermatitic epidermal nevus that should be distinguished from other inflammatory skin lesions such as CHILD nevus, linear psoriasis, and superimposed linear atopic dermatitis. A characteristic clinical feature of ILVEN is severe itching. If the nevus involves the ungual matrix, longitudinal or transverse depressions of the nail plate may be noted [239].

Linear psoriasis

Linear psoriasis reflects segmental mosaicism of this polygenic skin disorder. Superimposed linear psoriasis is characterized by early and pronounced involvement, being associated with bilateral, less severe non-segmental lesions [214]. Some cases of superimposed linear psoriasis with pronounced involvement of the nail plate have inadvertently been documented [240, 241].

Lichen striatus

If this linear skin disorder reaches the nail, longitudinal ridging as well as thinning and early splitting of the nail plate may be noted [242, 243].

Superimposed linear lichen nitidus

Boccaletti et al. [244] noted pronounced linear lesions of lichen nitidus in a 6-year-old boy who showed, in addition, a less severe disseminated bilateral involvement. The linear lesions had reached two fingers of his left hand and caused disturbed growth of the thumb nail (Fig. 9.51). This case can be taken as a further example of superimposed segmental manifestation of a polygenic skin disorder [214, 245].

Happle–Tinschert syndrome

This disorder is characterized by segmentally arranged basaloid follicular hamartomas, linear atrophoderma,
enamel defects, patchy hypertrichosis, and skeletal and cerebral abnormalities. The phenotype exclusively occurs sporadically and is caused by a postzygotic SMO mutation. Linear atrophoderma involving the thumb and resulting in nail dysplasia was described by Itin [246] in a 7-year-old boy.

Porokeratotic eccrine nevus

This linear nevus is also called “porokeratotic eccrine ostial and dermal duct nevus (PEODDN)”. Molecular analysis has shown that the disorder is caused by postzygotic GJB2 mutations and thus represents a mosaic manifestation of KID (keratitis, ichthyosis, deafness) syndrome [247]. In a 30-year-old woman, the nail plate of the involved index finger showed multiple shallow pits and a single longitudinal groove [248].

Linear porokeratosis groove

Among the various types of porokeratosis, the linear manifestation is not a specific entity. Rather, it should be
taken as a type 2 segmental involvement of one of these autosomal dominant disorders, usually of disseminated superficial actinic porokeratosis or of the plaque type of Mibelli [208]. By contrast, reports on a type 1 segmental manifestation are almost completely lacking because such mild involvement may often be overlooked. Kono et al. [249] described a 36-year-old man with systematized linear porokeratosis that could not be specified further. However, because the lesions were pronounced and present since childhood, a type 2 segmental manifestation is rather likely. The nail of the involved right first toe was dystrophic and showed irregular grooving and pterygium (Fig. 9.52). The disturbed nail growth had first been noted at elementary school age. Two similar cases of linear porokeratosis causing onychodystrophy had previously been reported [250, 251].

### Linear Darier disease

Darier disease is an autosomal dominant trait characterized by disseminated warty papules with the histopathological features of acantholytic dyskeratosis. The nails show longitudinal white or red lines. Moreover, nail fragility, splitting, or notching may occur. In type 2 segmental Darier disease, a pronounced linear involvement is superimposed on the ordinary non-segmental phenotype. In such cases, a more prominent ipsilateral nail involvement may be noted [252, 253].

### References


Chapter 9

Hereditary and Congenital Nail Disorders


Hereditary and Congenital Nail Disorders


Hereditary and Congenital Nail Disorders

363  Cluzeau C, Hadj-Rabia S, Jambou M et al. (2011). Only four genes (EDA1, EDAR, EDARADD, and WNT10A) account for 90% of hypohidrotic/anhidrotic ectodermal dysplasia cases. *Hum Mutat.* 32: 70–72.


Chapter 9


Hereditary and Congenital Nail Disorders


Hereditary and Congenital Nail Disorders


Hereditary and Congenital Nail Disorders


Hereditary and Congenital Nail Disorders


Chapter 10

Nail Disorders in Childhood

David de Berker1, Bianca Maria Piraccini2, Beth S. Ruben3, and Robert Baran4

1 Bristol Dermatology Centre, Bristol Royal Infirmary, Bristol, UK
2 Dermatology, Department of Experimental, Diagnostic and Speciality Medicine, University of Bologna, Bologna, Italy
3 Dermatology/Dermatopathology, University of California, San Francisco; Dermatopathology, Palo Alto Medical Foundation, Palo Alto, CA, USA
4 Hon. Pr. of the University of Franche-Comté; Nail Disease Centre, Cannes, France

Introduction

A classification of nail dystrophies according to age is somewhat arbitrary. Some nail diseases have a predilection for certain age groups but the relationships to age are usually not clearly defined. Certain abnormalities may be lifelong once acquired but their presentation may be modified by age, and the underlying pathology may worsen or improve with advancing years. Habits, occupation, and pastimes may have effects on the nail apparatus and are themselves influenced by the age of the patient.

Composition and morphology of the nail in childhood

Nail constituents

Nail plate analysis may be performed using a range of techniques and usually requires only a nail clipping (see Chapter 1). The normal levels of universal constituents have been examined, as have markers of disease and analysis of exogenous materials such as lead, narcotics, arsenic, etc., which may provide evidence of environmental pollution.

Pustular psoriasis and Hallopeau’s acrodermatitis continua, 307
Parakeratosis pustulosa (Hjorth–Sabouraud disease), 307
Nail lichen planus, 309
Lichen striatus, 309
Lichen nitidus, 311
Trachyonychia (twenty-nail dystrophy), 311
Alopecia areata of the nails, 313
Eczema, 313
Chronic paronychia, 314
Systemic diseases, 314
Cardiovascular disorders, 314
Gastrointestinal disorders, 315
Liver disorders, 315
Renal disorders, 315
Endocrine disorders, 316
Neurological disorders, 316
Hematological and lymphatic disorders, 316
Connective tissue diseases, 316
Immunological disorders, 317
Orthopedic and rheumatological disorders, 317
Nutritional disorders, 317
Psychiatric disorders, 318
Drug-induced nail disorders, 318
Benign tumors, 318
Melanonychia and melanoma, 318
Other malignant tumors, 322
Trauma, finger sucking, and nail biting, 322
Bullous eruption of the newborn, 322
Epidermolyisis bullosa, 323
Finger sucking, nail biting, and habit tic, 323
Nail degloving, 324
Infantile ingrown toenails, 325
Congenital malalignment of the great toenail, 325
Congenital hypertrophic lip of the hallux, 327
Grasp reflex multiple ingrown fingernails, 328
The chloride and sodium content of nails of normal newborns is highest at birth and decreases to 50% within 3 days [1]. The iron content of fingernails is variable in the same individual throughout the year [2]. The iron status of the individual is reflected by the amount of iron present in nail samples [3]. X-ray microanalysis of the fingernails showed a decrease in sulfur and aluminum, and a higher chlorine content in term infants than in preterm ones [4]. Elevated aluminum content in the nail of preterm infants may be a clue to the osteopenia observed in these infants [4]. Nail plate biopsies in neonatal anabolic disorders have been advocated by Lockard et al. [5]. The fact that ill neonates have a significantly lower nail nitrogen content than adults suggests a pattern of nail protein accumulation which parallels that of muscle and the whole body in the developing fetus and neonate.

Steroid sulfatase and its substrate, cholesterol sulfate, have been assayed in the nails of children being screened for X-linked ichthyosis and found to have adequate sensitivity and accuracy to be useful [6, 7]. The copper content in the hair and nails of patients with hepatolenticular degeneration (Wilson disease) is higher than normal [8].

In cystic fibrosis, the sodium and potassium content of nail clippings has been analyzed by Kopito et al. [9]; their concentrations in nails and hair were found to be elevated. Neutron activation analysis of sodium in nails [10] has proved to be a valuable diagnostic method in children over 1 year of age, showing that there is an increased concentration of sodium and potassium in the sweat of patients with cystic fibrosis; this is compatible with the idea that these ions are of extrinsic origin [11]. The immediate attraction of nail sodium analysis lies in its potential as a postal screening service [12]; however, the sodium content of nail clippings can be influenced by many factors, including the subject's activities for some time before the nails are cut. A simple, unified set of instructions before obtaining samples from small children may be necessary.

Analysis of nail clippings from the newborn by gas chromatography–mass spectroscopy can provide evidence of exposure to cocaine during embryogenesis. Given the point of nail formation, it is likely that the levels will reflect exposure after the 14th week [13].

Exposure to substances in the diet and through the environment can be measured in children, as in adults, through analysis of nail clippings. The protein content of the diet as reflected in isotopes of carbon and nitrogen in nail clippings has been used to compare tribal and gender differences in Papua New Guinea [14]. Arsenic levels are raised in hair and nail samples of children and adults in areas where groundwater levels of the element are increased [15], and this was found in children migrating to less contaminated areas such as those moving from Nicaraguan mining communities to Barcelona when compared with children born in the city [16, 17]. Fluoride is an important example, in which there is a desire to have sufficient to protect teeth but not to exceed this in order to avoid fluorosis. There is a range of potential sources of fluoride in our normal lives [18], and in particular these include toothpaste, food, and drink, including water. When nail can be sampled with ease at a low age, it can provide a useful means of assessment [19].

Microbiological contaminants can be determined from nail clippings and swabs beneath the nail, revealing a higher rate of meticillin-resistant Staphylococcus aureus in those with soft tissue infection and their careers when compared with a control group [20]. Conversely, keeping nails short and coupling this with a washing regimen has been shown to reduce the rate of parasitic gut infections in Ethiopian children with a corresponding increase in their mean hemoglobin [21]. Reducing the ability of the subungual space through clipping short has also been found to reduce the rate of spread of scabies in a Cameroonian boarding school, illustrating the role of nail as a fomite [22].

Nail morphology

Hudson et al. [23] measured index finger, nail, and thumb dimensions in normal, full-term infants within the first 3 days of life. In newborn infants the index fingernail length is $5.041 \pm 0.703$ mm and the width is $3.570 \pm 0.354$ mm. The thumb width is $9.800 \pm 0.546$ mm. These measurements are of potential value when describing syndromes in which nail shape and size are characteristically altered. One report suggests that about 75% of congenital syndromes are associated with nail abnormalities [24] (Table 10.1).

In infants and children with cardiopulmonary disease, measurements of the ratio of the distal phalangeal depth to the interphalangeal depth of the index finger have been performed. This measurement has been used to quantitate digital clubbing [23].

The length of nails is used as a morphological criterion for the assessment of gestational age in preterm babies [25, 26]. Premature infants may have nails that are shorter than the distal digital pulp, giving the appearance of distal ingrowing [27]. Work in adults suggests a relationship between the use of a hand in gripping and the flattening of the nail. The concept is that the pressure transmitted back through the digit pulp exerts a force on the lateral margins of the nail to counteract the natural degree of transverse curvature, so reducing it. The same work has not been done in children, although there is evidence that children with larger finger tips have reduced tactile acuity, which might correspond with use and altered shape of the digit [28]. Later in childhood lateral ingrowing can become a problem and may be in part
Nail Disorders in Childhood

caused by acquired or inherited anatomic changes contributing to deviation of the distal phalanx and the consequent asymmetric forces [29].

The five most common findings in otherwise normal children are: punctate leukonychia; onychophagia; pitting; koilonychia, especially of the great toe; and lamellar splitting of the free edge.

Table 10.1 Features of fingernails and toenails in infants.

<table>
<thead>
<tr>
<th>Feature</th>
<th>Fingernails</th>
<th>Toenails</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Width</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Micronychia: &lt;0.5</td>
<td>2 (3.8)</td>
<td>31 (59.6)</td>
</tr>
<tr>
<td>Macronychia: &gt;0.8</td>
<td>13 (25)</td>
<td>1 (1.9)</td>
</tr>
<tr>
<td><strong>Nail fold</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>“Pseudohypertrophy” of proximal nail fold</td>
<td>1 (1.9)</td>
<td>20 (38.4)</td>
</tr>
<tr>
<td>“Pseudohypertrophy” of lateral nail fold</td>
<td>4 (7.7)</td>
<td>38 (73.1)</td>
</tr>
<tr>
<td><strong>Shape</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Oval</td>
<td>36 (71.1)</td>
<td>2 (3.0)</td>
</tr>
<tr>
<td>Rectangular</td>
<td>10 (19.2)</td>
<td>13 (25)</td>
</tr>
<tr>
<td>Triangular</td>
<td>0 (0)</td>
<td>26 (50)</td>
</tr>
<tr>
<td>Round</td>
<td>5 (9.6)</td>
<td>11 (21.1)</td>
</tr>
<tr>
<td><strong>Plate</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Curvature</td>
<td>Convex</td>
<td>19 (36.5)</td>
</tr>
<tr>
<td></td>
<td>Concave</td>
<td>0 (0)</td>
</tr>
<tr>
<td></td>
<td>Koilonychia</td>
<td>0 (0)</td>
</tr>
<tr>
<td></td>
<td>Flat</td>
<td>33 (63.5)</td>
</tr>
<tr>
<td>Presence of lunula</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Punctuated leukonychia</td>
<td>0 (0)</td>
<td>2 (3.8)</td>
</tr>
<tr>
<td>Pigmentation</td>
<td>Homogeneous</td>
<td>46 (88.5)</td>
</tr>
<tr>
<td></td>
<td>Ingradation</td>
<td>6 (11.5)</td>
</tr>
<tr>
<td>Distal part</td>
<td>Onychoschizia</td>
<td>0 (0)</td>
</tr>
<tr>
<td></td>
<td>Onycholysis</td>
<td>6 (11.5)</td>
</tr>
<tr>
<td></td>
<td>Scales</td>
<td>11 (21.1)</td>
</tr>
<tr>
<td></td>
<td>Long nails</td>
<td>15 (28.8)</td>
</tr>
</tbody>
</table>

Data are no. (%).

Nail plate changes

Koilonychia

At birth the nail surface is smooth, shiny, and almost flat and the lunula is seldom visible. When depression of the nail plate is more marked, the appearance is that of koilonychia. In a study of 52 newborns, koilonychia was present in 33% as a normal variant affecting the great toe (Fig. 10.1a). An autosomal dominant pattern of inherited koilonychia is described by Gao et al. [30], although some variants are more akin to lichen planus with fissures and pterygium due to atrophy seen alongside some nails with more classic koilonychia [31]. When childhood lichen planus is the established diagnosis, it is apparent how the atrophy seen in this disease gives rise to the changes of koilonychia. Other diagnoses where nails may be thinned, such as Witkop tooth and nail syndrome, can result in some partial features of koilonychia [32]. There is also an increased prevalence of koilonychia attributed to microtrauma associated with barefoot walking and frequent water immersion [33].

Although koilonychia is common in healthy infants, it still has an association with iron deficiency and may be used as a clinical clue that may be noted before other clinical and laboratory signs of anemia develop [34]. It has been recorded as a clinical sign of anemia in childhood chronic Trichuriasis infection with dysentery when other features included growth retardation and sparse hair [35]. It may also be found in association with skeletal anomalies of unclear significance [36]. Weak nails may result from selenium deficiency [37].

Clubbing

Sometimes at birth, the nail curves over the tip of the digit towards the pulp; physiological clubbing may be seen in this age group. True congenital clubbing can
be associated with a benign familial presentation or congenital cardiac disease [38, 39]. More commonly, it is part of early evolving cyanotic cardiac problems or lung [40, 41] or bowel disease [42, 43]. Nasopharyngeal carcinoma presenting in childhood has been associated with clubbing in multiple instances [44] (Box 10.1).

**Lamellar splitting**

Lamellar splitting is a common finding in early infancy (Fig. 10.1b).

**Oblique markings**

In early childhood, fingernails often have oblique ridges that converge towards the center distally (Fig. 10.2a,b). These disappear in early adult life [45]. The appearance has been termed “chevron nail” [46–48] and “herringbone nail” [49], and subsequently debated [50]. It is not clear whether the distinction is of any real significance, although Shuster proposed that “chevron” was a preferable term because it does not imply the central spine implicit in the term herringbone. The semantics is debatable. While of no apparent medical significance, the pattern is difficult to explain in terms of matrix behavior and pattern formation. The authors favor the possibility that there is a limited transverse component to nail plate growth in childhood, in addition to the recognized longitudinal growth. Their combination results in narrow regions of oblique patterning that are not always symmetrical around a central longitudinal axis.

**Transverse depressions**

In the studies carried out by Turano [51], 92% of normal infants between 8 and 9 weeks of age had a single

---

**Box 10.1 Systemic diseases that may be associated with clubbing in children**

<table>
<thead>
<tr>
<th>Bilateral</th>
<th>Unilateral</th>
</tr>
</thead>
<tbody>
<tr>
<td>● Cardiac diseases</td>
<td>● Lower limb venous malformation</td>
</tr>
<tr>
<td>– Cyanotic congenital heart diseases (up to 30% of the children)*</td>
<td>● Klippel–Trénaunay syndrome</td>
</tr>
<tr>
<td>– Infective endocarditis</td>
<td>*May be associated with hypertrophic osteoarthropathy.</td>
</tr>
<tr>
<td>● Circulatory diseases</td>
<td>● Hodgkin disease with intrathoracic involvement*</td>
</tr>
<tr>
<td>– Abdominal arteriovenous fistula and polysplenia</td>
<td>– Mesothelioma of the pleura*</td>
</tr>
<tr>
<td>– Pulmonary arteriovenous malformations (up to 10% of the patients)</td>
<td>– Nasopharyngeal carcinoma*</td>
</tr>
<tr>
<td>● Lung diseases</td>
<td>– Osteosarcoma*</td>
</tr>
<tr>
<td>– Asthma</td>
<td>– Periosteal sarcoma*</td>
</tr>
<tr>
<td>– Bronchiectasis</td>
<td>– Rhabdomyosarcoma*</td>
</tr>
<tr>
<td>– Chronic lung infections</td>
<td>– Thymus carcinoma*</td>
</tr>
<tr>
<td>– Cystic fibrosis</td>
<td>● Hyperthyroidism*</td>
</tr>
<tr>
<td>– Intrathoracic tumors*</td>
<td>● Severe malnutrition</td>
</tr>
<tr>
<td>– Primary ciliary dyskinesia</td>
<td>● Celiac disease</td>
</tr>
<tr>
<td>– Pulmonary hemangioma</td>
<td>● Gastrointestinal tumors</td>
</tr>
<tr>
<td>● Liver diseases</td>
<td>– Inflammatory bowel disease</td>
</tr>
<tr>
<td>– Biliary atresia*</td>
<td>– Polyposis coli</td>
</tr>
<tr>
<td>– Chronic liver disease</td>
<td>● Infective diseases</td>
</tr>
<tr>
<td>– Hepatopulmonary syndrome with or without cirrhosis</td>
<td>– Chronic parasite infection (Trichuris trichiura, whipworm)</td>
</tr>
<tr>
<td>– Juvenile biliary cirrhosis</td>
<td>– HIV (cardiac and pulmonary complications secondary to AIDS)</td>
</tr>
<tr>
<td>– Wilson diseases</td>
<td>● Malignancies</td>
</tr>
<tr>
<td>● Gastrointestinal diseases</td>
<td>– Hodgkin disease with intrathoracic involvement*</td>
</tr>
</tbody>
</table>

(a) (b)

Figure 10.2 (a) Herringbone nail. (b) Temporary, oblique ridges of early childhood converging towards the center distally, here associated with pits.
transverse depression (Beau’s line) of the fingernails; this first appeared at the proximal portion of the nail as early as 4 weeks of age and grew out to the distal edge by 14 weeks of age. Beau’s lines of this type could be the result of malnutrition or other physiological disturbance, occurring during birth. Wolf et al. [52] reported Beau’s lines in all 20 nails of a female infant soon after birth; the transverse depressions extended through the entire thickness of the nail, which separated into two and gave rise to latent onychomadesis. The condition appears to have resulted from intrauterine distress (Fig. 10.3).

In childhood, cancer chemotherapy may produce serial Beau’s lines or transverse leukonychia reflecting the periodicity of treatment regimens.

Lamellar dystrophy is a common finding in children, although it has not been the subject of any reports. It is seen at both birth and later, particularly in the thumb and great toenail. It is unclear whether the change arises due to prolonged bathing and frequent wetting, which are considerations when the condition develops in adults. However, it may be limited to the thumb alone if it is habitually sucked. Thumb sucking can also contribute to chronic paronychia, which in turn may result in irregular transverse ridges and depressions in the nail plate.

Malalignment can occur in the great toe, as do a range of patterns of ingrowing. All these tend to alter the contour and thickness of the nail plate (Fig. 10.4) and are dealt with later in the chapter.

**Soft tissue features**

**Nail fold capillaries**

The adult nail fold capillary pattern matures rapidly during the first 3 months of life [53]; the loops appear in the neonatal period and their evolution during the first 3 months depends on weight (i.e. neonatal maturity) [54].

The normal nail fold capillary network in children resembles that observed in adults with some differences, such as lower number of loops per millimeter, a higher subpapillary venous plexus visibility score, and a higher frequency of atypical loops [55].

Monitoring children with Henoch–Schönlein purpura by nail fold capillaroscopy demonstrates the presence of abnormal capillary shapes in nearly half with a disturbance of vessel patterns and a variety of hemorrhages in 10%. Edema of the nail fold can be marked and is one of the more persistent features when the clinical complaint has subsided [56]. The same technique can be used to demonstrate abnormalities in inflammatory myopathies in childhood, and in particular variation with disease activity of features such as vessel dropout [57]. Kawasaki disease [58], dermatomyositis [59, 60], and scleroderma can all show altered nail fold capillaroscopy, in which in many instances it is prognostic [60, 61].

**Bacterial infections**

**Acute paronychia**

Acute paronychia may follow a break in the skin. It is a staphylococcal infection of the paronychium and usually affects the area of a hang nail, nail biting being the most common predisposing factor. Torn hang nail or other local injuries such as a thorn or splinter prick in a lateral nail groove enable bacterial inoculation that evolves rapidly towards pus collection. It also occurs frequently as an episode during the course of chronic paronychia when other organisms may be involved, including streptococcal, *Pseudomonas aeruginosa*, and coliform organisms and *Proteus vulgaris*.

Confusion can occur with infection (whitlow) caused by herpes simplex virus 1, in which surgical drainage is contraindicated. Cytological examination of Tzanck...
smear or viral polymerase chain reaction may be useful diagnostically. Orf virus and some fungi can also cause acute paronychia in children and adolescents.

The infection starts in the paronychium around the sides of the nail with local redness, swelling, and pain (Fig. 10.5). The treatment is twofold: administering penicillinase-resistant antibiotics and treating the acute paronychia surgically.

Localized superficial bulla bacterial infection close to the nail can be easily drained by incision with a pointed no. 11 scalpel without anesthesia. If the infection does not show clear signs of response to penicillinase-resistant antibiotics within 2 days, surgical intervention may be needed. A proximal block anesthesia in adolescents or general anesthesia in young children may reveal a narrow sinus. This sinus may be a part of a “collar-stud” abscess that communicates with a deeper necrotic zone, which must be laid open and excised. If the infection spreads to the nail bed, it may lift the nail. In this instance an avulsion of the proximal portion of the nail plate should be performed. A nail elevator is placed between the nail and nail bed to free the base of the nail. Then, the nail is split transversely just distal to the lunula, where the plate is not tightly attached to the subungual tissue.

A small piece of a water-soluble gauze is placed under the proximal nail fold to prevent adherence with a risk of scarring, while the finger is soaked three or four times a day in an antiseptic solution to facilitate drainage. This leads to rapid healing (8–10 days).

Sometimes if the finger is made numb by cooling with ethyl chloride or similar, drainage of superficial nail fold collections can be treated by pushing back the paronychium to drain the pus, followed by soaking the finger to maintain adequate drainage and administering antibiotics.

Complications of acute paronychia are rare but may include osteitis, which can in turn rarely require amputation. Acquired periungual fibrokeratoma after staphylococcal paronychia has been reported. As trauma and terminal phalanx fractures can mimic acute paronychia, radiography is advised when the latter occurs after trauma.

Impetigo

The dorsal aspect of the distal phalanx may be involved by impetigo (Fig. 10.6). It comes in two forms:

- vesiculopustular with its familiar honey-crusted lesions, usually due to β-hemolytic streptococci
- bullous, usually due to phage type 71 staphylococci (develops on intact skin).

The latter is characterized by the appearance of large, localized, intraepidermal bullae that persist for longer periods than the transient vesicles of streptococcal impetigo, which subsequently rupture spontaneously to form very thin crusts. The lesions of bullous impetigo may mimic the non-infectious bullous diseases such as drug-induced bullae.

![Figure 10.5 Acute paronychia.](image)

![Figure 10.6 (a) Impetigo involving the proximal nail fold with subsequent onychomadesis. (b) Impetigo of the distal digit, surrounding the nail. (c) Honey-crusted lesion involving the nail bed, before and after 1 month of penicillinase-resistant penicillin treatment.](image)
Oral therapy of bullous impetigo with cloxacillin should be instituted and continued until the lesions resolve. Cefprozil and clarithromycin are acceptable substitutes. The lesions should be cleansed several times daily and topical mupirocin ointment rubbed into all the affected areas.

Poorly trimmed nails may serve as a paronychial focus for infection in children during chemotherapeutic treatment for various malignant disorders [62]. Intense scratching of infected atopic dermatitis coupled with minor trauma to the fingertips have been found to create distal subungual microabscesses that spread contiguously to the underlying bone [63].

Blistering distal dactylitis

Blistering distal dactylitis (BDD) is a variant of streptococcal skin infection (Fig. 10.7). This condition presents as a superficial, non-tender, blistering, \( \beta \)-hemolytic streptococcal infection over the anterior fat pad of the distal phalanx of the finger [64]. \( S. \text{ aureus} \) and \( Staphylococcus \text{ epidermidis} \) are isolated less frequently. \( S. \text{ aureus} \) may be characterized by involvement of multiple digits [65] and is thought to be becoming more common as a cause of BDD [66]. The lesion may or may not have a paronychial extension and more than one digit is frequently involved [67]. This blister with an erythematous base, containing thin, white pus, has a predilection for the tip of the digit. It extends to the subungual area of the free edge of the nail plate. This area may provide a nidus for bacteria and act as a focus of chronic infection [68], which may also be found on swabbing the pharynx. Recurrent blistering dactylitis has also been reported with ingrowing toenail [69]. The age range of affected patients is 2–16 years. The condition is exceptionally reported in adults: a healthy fishmonger [70]; another case due to \( S. \text{ aureus} \) in an immunosuppressed patient [72].

Local care entails incision and drainage of the thin white pus. Antiseptic soaks facilitate the response to systemic antibiotics: effective regimens include penicillin G in a single intramuscular dose or a 10-day course of oral phenoxymethylpenicillin, a macrolide, or augmentin. Antiseptic and systemic therapy combined may decrease the reservoir of streptococci by preventing spread to family contacts [73, 74]. In a 6-month-old infant, bacterial culture grew meticillin-resistant \( S. \text{ aureus} \) that responded to vancomycin administration [75].

Non-blistering dactylitis may be infective or sterile. Tuberculous dactylitis has been reported in a Chinese child [76] and \( Haemophilus \) infection superimposed on dactylitis seen in sickle cell disease is also recognized [77]. Sickle cell disease [78] and forms of juvenile or psoriatic arthritis [79] are the main non-infective forms of dactylitis seen in childhood.

The differential diagnosis includes blisters resulting from friction or thermal and chemical burns, which can raise concerns about how the child sustained the injuries. Other diagnoses include infection such as herpetic whitlow and staphylococcal bullous impetigo and the Weber–Cockayne variant of epidermolysis bullosa.

Toxic shock syndrome

In this \( S. \text{ aureus} \) infection with fever, children present with hypotension, generalized erythema, diarrhea, and central nervous system and electrolyte abnormalities. Hair and nails may shed about 2 months following the acute illness [80].

Veillonella infection of the newborn

Forty-two outbreaks of subungual infection were described by Sinniah et al. [81] among infants in postnatal wards and special care baby units (Fig. 10.8). The number of fingers affected per patient ranged from one to 10; the thumbs were less frequently involved than other digits, and the toenails were spared altogether. Three stages were found. First, a small amount of clear fluid appears under the center of the nail, along with mild inflammation at the distal end of the finger. This initial vesicle lasts approximately 24 h; it sometimes enlarges but never to the edge of the nail. Some small lesions bypass the second, pustular stage, going directly into the third stage. As a rule, the fluid becomes yellow after 24 h, the pus remaining for 24–48 h before gradually turning brown, and being absorbed. This color fades progressively over a period of 2–6 weeks, leaving the nail and nail bed apparently completely normal. Subungual pus obtained by aseptic puncture of the nails showed tiny, Gram-negative cocci in a patient with insulin-dependent diabetes [71]; and another case due to \( S. \text{ aureus} \) in an immunosuppressed patient [72].
about 0.4µm in diameter. These organisms resembled *Veillonella*, bacteria of dubious pathogenicity and the most common anaerobes to be found in the saliva of adults [82]. In neonates, *Veillonella* is more common in the bowel of bottle-fed than breast-fed children and this is compatible with those on intensive care units [83]. It is also found in the vagina and respiratory tract.

**Other bacterial infections**

Anaerobic infections (*Bacteroides*, *Bacillus fragilis*, and *Fusobacterium*) may affect many sites, including the fingers and nail beds [84]. In the newborn, nursery epidemics of staphylococci produce cases of omphalitis, mammary abscess, dacryocystitis, or paronychia. The localization is probably due to the presence of a locus minoris resistentiae, with trauma perhaps being a factor in paronychia [85].

In Leiner disease (Fig. 10.9) recurrent paronychia infections and interdigital intertrigo (usually due to Gram-negative bacteria) may be only some of the many infective episodes observed [85]. Topical clindamycin is usually effective.

In childhood, local trauma, caused by onychophagia, may result in the development of opportunistic infection by the normal oropharyngeal flora, resulting in acute paronychia. This may be caused by BH 1 organisms (*Eikenella corrodens*). It is uncommon in the absence of an immune deficiency [86].

In Leiner disease (Fig. 10.9) recurrent paronychia infections and interdigital intertrigo (usually due to Gram-negative bacteria) may be only some of the many infective episodes observed [85]. Topical clindamycin is usually effective.

In childhood, local trauma, caused by onychophagia, may result in the development of opportunistic infection by the normal oropharyngeal flora, resulting in acute paronychia. This may be caused by BH 1 organisms (*Eikenella corrodens*). It is uncommon in the absence of an immune deficiency [86].

It is important to remember that the nail matrix is very susceptible to infection in early life and may be irreversibly damaged within 48h of the onset of acute infection. This means that rapid intervention is required and it is of value to relieve pressure developing beneath the nail if there is a collection of pus. Not only will this reduce the chance of pressure necrosis of the matrix, but it will also give pain relief.

**Fungal infections**

See Chapter 12.

**Dermatological diseases**

Children have the same dermatological diseases as seen in adults, but there are several differences regarding prevalence, clinical features, severity, and modality of treatment. Moreover, there are some dermatological conditions that are typical/exclusive in childhood, such as parakeratosis pustulosa and lichen striatus.

**Nail psoriasis**

Nail psoriasis in children is uncommon. Nail involvement is reported in 19–32% of the children with other forms of psoriasis [87, 88], and isolated nail psoriasis accounts for 0.11% of pediatric dermatology consultations [87]. Nail involvement is associated with male sex, palmoplantar psoriasis, severity of disease, and psoriatic arthritis [88].

The nail signs are the same as described in adults (see Chapter 14), with the most common sign being pitting, usually seen in the fingernails. The nail plate surface shows multiple depressions, which are typically irregular in size, depth, and distribution (Fig. 10.10). In children, pitting is usually mild and limited to one or to a few digits (Fig. 10.11), and it is only rarely associated with other signs of nail psoriasis (Fig. 10.12). The second most common sign of nail psoriasis in children is onycholysis associated with subungual hyperkeratosis (Fig. 10.13), mainly observed in the toenails. The oil drop sign is rare in children, as is the erythematous border surrounding onycholysis. Nail plate thickening involving several toenails that are difficult to trim is another common sign of presentation of nail psoriasis at a very young age (Fig. 10.14). Nail psoriasis in children...
may also present as trachyonychia (Fig. 10.15), clinically not distinguishable from trachyonychia due to other inflammatory diseases. Rarely, nail psoriasis is severe, with involvement of several nails and marked nail changes (Figs 10.16, 10.17).

As trauma worsens psoriasis through the Koebner phenomenon, fingernail signs are more severe in children who bite their nails (Fig. 10.18). Psoriatic arthritis is less common than in adults, but its occurrence should be not underestimated in children (Fig. 10.19).

Figure 10.10 Nail pitting in childhood. Psoriasis pits are irregular in size and distribution, some are covered by scales.

Figure 10.11 Pitting of a few digits in childhood psoriasis.

Figure 10.12 Mild nail pitting associated with splinter hemorrhages and onycholysis.

Figure 10.13 Nail psoriasis in children: onycholysis and subungual hyperkeratosis.
Differential diagnosis of childhood nail psoriasis includes other diseases that cause onycholysis and subungual hyperkeratosis, mainly distal subungual onychomycosis and eczema. Onychomycosis is rare in children, in whom it can be limited to a single digit, including fingernails [89]. The nail signs may be clinically indistinguishable from those of nail psoriasis, and differential diagnosis can be impossible without mycology. Eczema in childhood is commonly due to atopic dermatitis, which can involve the...
Nail Disorders in Childhood

Figure 10.19 Psoriasis of the thumb associated with psoriatic arthritis of the distal interphalangeal joint in a 9-year-old girl.

Figure 10.20 Hallopeau’s acrodermatitis continua in a 12-year-old girl: onycholysis and subungual hyperkeratosis typical of the subacute phase.

Hand and the periungual tissues, causing mild onycholysis and subungal hyperkeratosis. Nail signs are always associated with dermatitis of the dorsal or volar skin of the hand. Nail thickening with increased transverse curvature due to severe nail bed hyperkeratosis with onset in childhood is a typical finding of pachyonychia congenita, in which all 20 nails are involved with different degrees of severity. The family history and the associated findings lead to the diagnosis.

Management of nail psoriasis in children is not easy, as most of the commonly utilized therapies for nail psoriasis are not adequate in children, due to the risk of side effects. Pitting and mild forms of onycholysis and subungal hyperkeratosis may benefit from urea-containing creams or lacquers, to smooth the nail plate surface and reduce toenail thickening. Topical therapies may be effective in nail bed disease and include combinations of steroids and calcipotriene, tazarotene [90], and high-potency topical steroids.

Although systemic therapies, including biologicals, have been used in nail psoriasis in children [91], their prescription should be restricted to severe cases not responding to conventional therapies.

Pustular psoriasis and Hallopeau’s acrodermatitis continua

Hallopeau’s acrodermatitis continua is rare in children and pustular psoriasis is exceptional. The nail changes are the same described in adults (see Chapter 14). Hallopeau’s acrodermatitis continua involves one or two digits, with recurrent painful episodes of sterile pustules arising in the nail bed and periungual skin. The chronic relapsing course impairs healing between the episodes, with erythema and scaling remaining in the subacute phase (Fig. 10.20).

Diagnosis is easy in the acute phase, while the clinical history of recurrent pustular episodes in the same digit is mandatory for diagnosis in the subacute phase. Differential diagnosis mainly includes herpes simplex infection.

Treatment depends on the severity of symptoms. Mild forms may benefit from association of steroids and vitamin D derivatives. Ultraviolet B therapy has been successfully used in two cases, with one in association with thalidomide [92, 93]. Adalimumab induced complete resolution of skin and nail symptoms in a 9-year-old girl with Hallopeau’s acrodermatitis continua not responsive to steroids, ciclosporin, and etanercept [94].

Parakeratosis pustulosa (Hjorth–Sabouraud disease)

This is a disease that is typical in and exclusive for children; it occurs in girls more than in boys, with a peak age of 5–7 years. A single digit of the hand, often the thumb or index finger, more commonly on the right hand than the left, presents with mild eczematous changes of the pulp associated with psoriasiform nail changes (Figs 10.21, 10.22) [95]. Vesicles or pustules are seen early in the development of the disease. A subacute eczematous eruption consisting of erythema and scales then develops in the affected digit and often precedes the nail changes. In the nail, the clinical changes are a mild distal or lateral subungal
hyperkeratosis and onycholysis. Nail plate pitting, thickening, transverse ridging (Beau's lines), and discoloration can occur (Fig. 10.23).

The differential diagnosis includes onychomycosis, thumb sucking, and eczema. A dermatophyte infection should be considered if the nail changes predominate, especially on the feet. Thumb sucking should be ruled out when a single thumb is affected. Patch tests are suggested to rule out contact dermatitis.

Periungual skin biopsy usually shows a spongiotic dermatitis, although psoriasiform changes may be observed (Fig. 10.24).

Parakeratosis pustulosa has a chronic course and tends to improve with time. Some children develop a frank nail psoriasis. For this reason, the condition is considered a variant of nail psoriasis of childhood [95, 96].

Treatment includes topical application of low-potency steroids and/or vitamin D derivatives on skin eczema and on the affected nail bed when onycholysis is present.

Figure 10.21 Parakeratosis pustulosa: eczematous changes of the distal pulp associated with onycholysis and subungual hyperkeratosis involving one finger.

Figure 10.22 Parakeratosis pustulosa. (a) Clinical features. (b,c) Histology. Courtesy of J.M. Mascaro.

Figure 10.23 Parakeratosis pustulosa: pitting and nail plate surface abnormalities more marked on one side of the nail.

Figure 10.24 Parakeratosis pustulosa: eczematous changes of the distal pulp associated with onycholysis and subungual hyperkeratosis involving one finger.
Nail Disorders in Childhood

Nail lichen planus

Nail involvement by lichen planus is less common in children than in adults, occurring in about 14–20% of patients with skin lichen planus [97, 98]. As in adults, even in children lichen planus may be limited to the nails (see Chapter 14). Other differences in nail lichen planus in children versus adults include a milder severity in children, in whom matrix scarring is unusual; a more frequent association of childhood lichen planus with autoimmune disorders; and a less common association of lichen planus with oral or cutaneous disease in children [98–101].

Nail lesions are usually mild with several/all nails showing thinning and longitudinal fissures with distal nail splitting (Fig. 10.25). Nail bed involvement with mild onycholysis and subungual hyperkeratosis is another possible presentation. Onychomadesis of a few nails has been reported as a nail sign associated with skin lichen planus in two children [102].

Diagnosis is optimized by a longitudinal nail biopsy. Although in most cases the lichenoid inflammatory infiltrate is centered on the nail matrix, any portion of the nail unit may be affected.

Treatment is based on systemic steroids, in order to avoid a scarring outcome with pterygium formation. Either oral prednisone 0.5 mg/kg or intramuscular triamcinolone acetonide 0.5–1 mg/kg/month can be prescribed for 4–6 months. Response to therapy is higher in children than in adults, but recurrences occur in up to 50% of cases [100].

Lichen striatus

Lichen striatus is a rare, benign, self-limited linear dermatosis of unknown origin that follows the lines of Blaschko. The condition is most common in children aged 3–10 years but can occur from 6 months to 12 years of age [103]. It is more common in boys. The etiology of lichen striatus is unknown. It presents as the sudden onset of linearly distributed tan or flesh-colored lichenoid papules along the entire length of an extremity, reaching distally the proximal nail fold and nail plate (Figs 10.26, 10.27). It usually involves just one finger, usually the thumb. Skin lesions may develop before or after the appearance of the nail changes. Nail changes due lichen striatus may also occur without cutaneous
lesions, making the diagnosis difficult and the condition probably underestimated. In the published cases with isolated nail involvement, the diagnosis was made based on the clinical appearance, spontaneous clearing of the nail abnormalities, and the histopathological findings [104].

Clinical signs of nail involvement include longitudinal fissuring, thinning, and distal splitting more marked in one side of the nail (Figs 10.28, 10.29a) [104–106]. The thumb is most frequently involved [103]. Involvement of two adjacent nails is rare.

The differential diagnosis of lichen striatus includes linear psoriasis and linear lichen planus.

Histopathology shows a band-like lymphocytic infiltrate in the superficial dermis of the nail matrix, with exocytosis, spongiosis, and focal hypergranulosis of the epithelium [103, 104].
Lichen striatus regresses spontaneously in a few years (Fig. 10.29b) [104], although some cases with long-lasting course have been reported [107]. A case of pterygium following matrix destruction has also been reported [108].

Cutaneous changes may benefit from topical therapy with tacrolimus or combining a retinoid with a steroid [109, 110].

Lichen nitidus

Lichen nitidus is an uncommon chronic skin eruption affecting children and young adults characterized by grouped asymptomatic skin-colored tiny papules mainly located on the arm, chest, and abdomen. Nail changes in lichen nitidus are rare and only seven cases have been reported in the literature [111–117]. The usually precede development of skin lesions, which may lead to delayed diagnosis. Reported nail changes include pits, longitudinal ridges, and fissures, which may be associated with swelling and hyperpigmentation of the proximal nail fold. Bettoli et al. [116] reported a case of a 10-year-old boy with generalized lichen nitidus, oral involvement, and nail changes characterized by longitudinal striations and pits on the fingernails and transverse ridging of the great toes. In a case of lichen nitidus restricted to the nails with giant cells at histopathology, lichen planus could not be ruled out [118].

Treatment is not required.

Trachyonychia (twenty-nail dystrophy)

Twenty-nail dystrophy was the term coined by Hazelrigg et al. [119] to describe an entity already recognized by Samman [120] as “excess ridging” of childhood. The condition was then termed “vertical striated sandpapered 20-nail dystrophy” [121] and, finally, “trachyonychia” by Alkiewicz [122] and then Achten and Wanet-Rouard [123]. The name trachyonychia is now preferred as it describes a particular clinical appearance characterized by roughness and opacity of the nail plate, with brittleness and terminal splitting, which can be due to different conditions that cause mild inflammation of the proximal nail matrix. Trachyonychia is not a disease per se, but a clinical sign. The name trachyonychia is also preferred to “twenty-nail dystrophy” as the condition does not necessarily affect the 20 nails (Box 10.2).

Trachyonychia is much more common in children, with a gradual insidious onset and peak age of 3–12 years, even if onset in adults is possible. In children, several or all nails are usually affected and are usually not associated with other diseases (“idiopathic trachyonychia”) [124]. However, there is overlap with the nail plate changes associated with alopecia areata [125]. Common causes of trachyonychia include alopecia areata, in which trachyonychia occurs in more than 3% of the patients [125], lichen planus [98, 99], psoriasis, and atopic dermatitis [126–129]. Other possible causes include ichthyosis vulgaris, pemphigus vulgaris, and other diseases [128, 129].

The clinical features of trachyonychia vary in severity from patient to patient, and often vary in the different nails of the same patients. One, several, or all nails can be involved, with fingernails affected more commonly than toenails. Morphologically, there are two main types: opaque and shiny trachyonychia [121]. In the first type the nail appears longitudinally striated with a sandpapered appearance and covered with minute scales rendering the nail opaque (Figs 10.30–10.33). In the second type, all 20 nails are shiny, as they present multiple minute pits oriented in longitudinal striae that reflect light (Figs 10.34, 10.35). Koilonychia due to nail plate thinning and hyperkeratosis of the cuticles is often associated with both varieties. The two types can be seen in the different nails of the same patient (Fig. 10.36).

Only some reports include histological data. We have found, in children, either vacuolated cells with intercellular and intracellular edema in the nail bed epidermis and squamous cells of the matrix presenting with homogeneous pale staining, or changes typical of lichen planus. Scher et al.
Figure 10.30 Opaque trachyonychia: the nails are opaque and vertically striated.

Figure 10.31 Opaque trachyonychia: the nails are opaque and vertically striated.

Figure 10.32 Opaque trachyonychia of the nails. Dermoscopy shows the longitudinal scaling of the superficial nail plate.

Figure 10.33 Opaque trachyonychia involving all 20 nails.

Figure 10.34 Shiny trachyonychia: multiple small pits oriented longitudinally.
Nail Disorders in Childhood

313

reported one case that showed microscopic evidence of lichen planus. Silverman and Rhodes [131] saw a child with oral lichen planus who had twenty-nail dystrophy. Donofrio and Ayala’s [132] patient showed psoriasiform epithelial hyperplasia with hypergranulosis. Wilkinson et al. [133] presented histopathological findings that were incompatible with the definition of the condition as a variant of lichen planus; there was considerable distortion of the nail matrix with a fairly dense mononuclear inflammatory infiltrate below and within the matrix epithelium, together with marked spongiosis. No basal cell liquefaction was present. These changes suggested an eczematous picture. Alkiewicz [122] found similar histological findings in two cases in which roughness of the nails had been induced by strong chemicals and in a third case involving all 20 nails with no obvious cause. Examination of nail biopsy specimens may therefore rule out lichen planus and psoriasis restricted to the nails. Braun-Falco et al. [134] reported spongiotic dermatitis of the nail matrix and the nail bed with column-like parakeratosis within the nail in trachyonychia, due to alopecia areata, atopic dermatitis, and the idiopathic form. In those subjects with no obvious cause and histological evidence of eczematous changes, alopecia areata has occurred in some cases. Jerasutus et al. [135] studied five cases, the youngest being 15 years old. The course is chronic with a tendency to spontaneous improvement, which has been reported in 50% and 82% of the children in two different series [136, 137].

Although in most cases the diagnosis is made clinically, and a biopsy is not often obtained in this setting, as the condition is usually self-limited and resolves without scarring, it can serve to better elucidate the underlying cause if treatment is sought. The histological features in trachyonychia vary with respect to the underlying etiology as noted above, but the spongiotic inflammatory pattern is the most common [124]. In eczematous disease and alopecia areata, a biopsy may demonstrate spongiosis of nail unit epithelium. When the cause is lichen planus, a lichenoid lymphohistiocytic infiltrate and necrotic keratinocytes can be found anywhere along the nail unit epithelium. In later phases of lichen planus, atrophy of the nail unit and scarring may result, but this does not generally occur in the setting of trachyonychia. In alopecia areata, features of lichen planus have also been reported [125]. In psoriasis, typical findings of psoriasiform epidermal hyperplasia, with subungual parakeratosis, serum, and neutrophils, and sometimes small neutrophilic pustules and hemorrhage can be observed. There may be characteristic vascular changes of dilated blood vessels abutting the junctional zone of the epidermis. Hypergranulosis rather than hypogranulosis may be seen, and sometimes the histological findings are subtle [138, 139].

Treatment can be necessary for cosmetic purposes or in cases with severe nail thinning and distal nail plate fragility: emollient or nail lacquers can be used in mild cases [140], while topical steroids can be tried in more severe cases. A recent study reported a beneficial effect of calcipotriol/betamethasone ointment applied on the proximal nail fold, with 98.6% of the treated nails achieving total clearance after 6 months of therapy [141].

Alopecia areata of the nails

See Chapter 15.

Eczema

See Chapter 15.
Chronic paronychia

Chronic paronychia is not uncommon in children. It differs from the condition seen in adults in the source of the maceration, associated diseases such as atopic dermatitis [142], the clinical appearances of the lesion, and the patients’ responses to their symptoms [143]. There is some evidence linking frequency of pediatric chronic paronychia with type 1 diabetes [144]. Chronic paronychia in children is usually severe with total involvement of the proximal nail fold. The skin is usually erythematous and glistening due to the wet environment produced by continuous thumb sucking. The nail plate shows surface abnormalities as Beau’s lines (Fig. 10.37).

When the acute flare occurs, the patient with atopic dermatitis experiences pruritus and discomfort in the proximal nail fold and evident inflammatory changes. Children respond to this by sucking, perpetuating the symptoms of chronic paronychia and the habit which initiates the maceration. The severity in children may reflect the irritant quality of saliva and the fact that exposure may be all night long [145]. Also, the threshold for an irritant reaction may be less in some children than in adults; this applies particularly to atopics (Fig. 10.38). The eczematous background to many cases of paronychia emphasizes the need to treat it primarily as a localized dermatosis rather than an infection, in spite of the presence of Candida.

Multiple persistent and repeated paronychia in infancy can represent a more serious underlying disorder, and such infants should be investigated for endocrine disease, immune deficiency syndromes, and systemic disease such as histiocytosis X, acrodermatitis enteropathica, and reactive arthritis.

Therapy for childhood paronychia should first be directed at drying the affected digits. The near impossibility of preventing thumb sucking makes it difficult. Clotrimazole applied several times daily when Candida is suspected and topical clindamycin solution can be helpful. The latter kills bacteria, has a bitter taste to discourage further sucking, and has an alcohol propylene glycol vehicle that dries out residual moisture. An alternative approach employs the use of topical steroids in combination with antimicrobials; this is useful when much of the clinical complaint arises through the inflammation of the nail folds, which is slow to settle on antimicrobial therapy alone.

Systemic diseases

Cardiovascular disorders

Congenital heart disease
See Chapter 15.

Infective endocarditis
Clubbing is one of the most common signs of heart disease in children [146] and it can be the presenting sign of infective endocarditis. A study on 2039 children and adults in emergency room presentations put clubbing among clinical signs highly indicative for infective endocarditis [146].

Kawasaki disease (mucocutaneous lymph node syndrome)
See Chapter 15.

Henoch–Schönlein purpura
Proximal nail fold videocapillaroscopy performed in the acute phase of Henoch–Schönlein purpura in 31 children showed moderate to massive edema and reduced capillary density with disarranged capillaries of abnormal shape and length. After 6 months edema remained in all patients, while morphological changes persisted in only two, suggesting incomplete disease resolution at a microvascular level [147].

Purpura fulminans
Acute infectious purpura fulminans is a rare life-threatening emergency that follows 7–10 days of overwhelming sepsis due to meningococcus or S. aureus. The primary
features are large purpuric skin lesions, fever, hypotension, and disseminated intravascular coagulation. Symmetrical gangrene of the extremities is a common sequela, associated with a mortality rate of 20–25%. Survival in purpura fulminans is not dependent on surgery, and surgery does not play a key role in the early phase of the disease. However, early surgical consultation to assess whether limb perfusion can be improved to achieve limb salvage is still absolutely necessary [148].

**Stimulator of interferon genes-associated vasculopathy with onset in infancy**

Stimulator of interferon genes (STING)-associated vasculopathy with onset in infancy (SAVI) is an autoimmune disease caused by gain-of-function mutations in TMEM173, which is critical for innate immune function. Between 2 weeks and 6 months of age, affected children develop a telangiectatic, pustular, or blistering rash on the cheeks, nose, fingers, toes, and soles due to leukocytoclastic vasculitis and microthrombotic angiopathy. Over time, signs of small-vessel damage develop, including nail fold capillary tortuosity and capillary loop loss, dystrophic nail changes, resorption of distal phalanges of fingers and toes, and digital gangrene with autoamputation [149].

**Gastrointestinal disorders**

**Celiac disease**
See Chapter 15.

**Inflammatory bowel disease**
Acquired digital clubbing may be seen in children with Crohn’s disease and ulcerative colitis [150]. Possible pathogenetic mechanisms for this digital malformation include mucosal inflammatory change and fibrosis mediated by the vagus and possibly other autonomic pathways acting as the afferent arc of a finger-clubbing reflex. Presence and severity of clubbing are indicators of disease activity. Multiple pyogenic granulomas of the nail bed have been described in one 17-year-old girl prior to clubbing development [151].

Arterial embolism of a finger leading to gangrene has been reported in one child with inflammatory bowel disease, due to the increased risk of thromboembolism associated with the condition [152].

**Peutz–Jeghers syndrome**
See Chapter 15.

**Liver disorders**

**Cirrhosis**
Clubbing occurred in 8.5% of 120 children with cirrhosis and was significantly higher in those patients in whom cirrhosis was associated with hepatopulmonary syndrome [153]. Clubbing was associated with onycholysis, surface nail abnormalities, and leukonychia in a 6-year-old girl with cirrhosis. Complete regression of nail changes was seen after liver transplantation [154].

**Spontaneous liver cell adenoma**
Koilonychia was reported as an unusual finding in a series of five children with liver cell adenoma [155].

**Wilson disease**
See Chapter 15.

**Renal disorders**

**Renal failure – hemodialysis**
See also Chapter 15.

Half-and-half nails and other nail changes are common in children in hemodialysis [156]. Half-and-half nails are seen in about 20–30% of patients, especially in those with diabetes. In half-and-half nails the proximal area of the nail is dull white and the distal area is pink or reddish brown, with a distinct border between the two colors (Fig. 10.39).

**Nail changes in renal transplant recipients**
See also Chapter 15.

Muehrcke’s lines and true leukonychia are common in children who have undergone kidney transplantation, as they are in adults [157]. Lamellar onychoschizia has been reported in one-third of the cases in another series [158].

**End-stage renal disease**
Calciphylaxis in children is extremely rare, and only a few cases of digital gangrene in children with end-stage renal disease have been reported in the literature [159, 160]. Hyperesthetic pain is a sentinel symptom, and
Endocrine disorders

Diabetes
See Chapter 15.

Parathyroid disease
Nail pitting associated with broad thumb and brachydactyly were reported in a 10-year-old child with papilledema as the presenting feature of pseudohypoparathyroidism [161].

Pituitary disease
In cerebral gigantism, or Sotos syndrome, excessive growth is associated with distinctive craniofacial features, developmental delay, and nail brittleness, as reported in two of 22 adolescent patients [162].

Thyroid disease
Nail signs in children with hypothyroidism are the same as those described in adults (see Chapter 15), even if rarely reported in the literature. Brittle nails and slow nail growth are common in hypothyroidism at any age and may also be seen in congenital hypothyroidism [163].

Plummer’s nails have been reported in an adolescent girl [164]. Thyroid acropachy can be seen in children: digital clubbing is associated with soft tissue swelling of the hands and feet and periosteal new bone formation [165].

Neurological disorders

Carpal tunnel syndrome
See also Chapter 15.
Carpal tunnel syndrome is very rare in children, and is mainly seen in hereditary and genetic forms, i.e. mucopolysaccharidosis [166] and in Down syndrome. Other causes include excessive hand trauma due to sports (golf, weight lifting, and basketball), trauma, and local tumors.
Hand clumsiness and thenar hypoplasia rather than sensory complaints are the presenting symptoms in children, making the diagnosis often delayed. The most common clinical features are non-healing ulcers of the distal digit, involving the index, middle, or ring fingers associated with nail changes, including Beau’s lines, nail thickening, and striate leukonychia. Acroosteolysis is rare [167, 168].

Congenital insensitivity to pain
See Chapter 15.

Hematological and lymphatic disorders

Anemia
See Chapter 1.
of children with dermatomyositis also have Gottron’s papules (knuckle pads), i.e. symmetric, pink to violaceous, papular lesions on the dorsal aspect of metacarpophalangeal and interphalangeal joints (Fig. 10.42), elbows, patellae, and medial malleoli, which are pathognomonic of the disease.

The so-called scleroderma pattern, characterized by the presence of avascular areas and enlarged or giant loops, is seen in about 50% of children with mixed connective tissue disease, and in 90% of children with systemic scleroderma [172, 173]. A follow-up study on nail fold capillaroscopy in 150 children and adolescents with primary Raynaud phenomenon showed that the presence of the sclerodermatous type of capillary changes has a high prognostic value of development of scleroderma spectrum disorders [177].

**Immunological disorders**

**Primary immunodeficiency disorders**

In primary immunodeficiency disorders there is a poor or absent function in one or more components of the immune system, resulting in an increased susceptibility to infections. Nail changes are usually caused by fungal infections, due to *Candida* and dermatophytes. Chronic candidiasis of the nails has been reported in 59% of patients with familial autosomal dominant hyper-immunoglobulin (Ig) E syndrome [178, 179]. Total dystrophic onychomycosis due to *Candida* and/or dermatophytes associated with skin and mucous membrane infection is a typical feature of chronic mucocutaneous candidiasis. A case of trachyonychia in a child with selective IgA deficiency has been reported, where association may be coincidental [180].

**Graft-versus-host disease**

See also Chapter 15.

Nail involvement is reported in about half of the children with graft-versus-host disease, more commonly in association with the sclerotic variant, and is considered a poor prognostic factor [181]. Nail changes may occasionally precede the development of graft-versus-host disease. Nail abnormalities resemble those of nail lichen planus, with longitudinal ridging and distal splitting and dorsal pterygium (Fig. 10.43).

**Orthopedic and rheumatological disorders**

**Chronic recurrent multifocal osteomyelitis**

See Chapter 15.

**Adult-onset Still disease**

A doubtful diagnosis of adult-onset Still disease or systemic juvenile idiopathic arthritis sine arthritis was made in two adolescents with an acute illness characterized by spiking fever, malaise, myalgia, arthralgia, leukocytosis, and itchy linear erythematous lesions and splinter hemorrhages of the nail beds [182].

**Nutritional disorders**

See also Chapter 15.

**Iron deficiency**

Koilonychia and nail bed pallor can be seen in children and adolescents with iron deficiency [183]. Nail bed pallor is considered 85% sensitive and 41% specific in indicating acute anemia due to malaria in children of less developed countries [184].

---

**Figure 10.42** Juvenile dermatomyositis: Gottron’s papules on the interphalangeal joints.

**Figure 10.43** Graft-versus-host disease: dorsal pterygia of several nails.
Selenium deficiency
See Chapter 15.

Zinc deficiency
In children, zinc deficiency may be primary, due to dietary inadequacy (older breast-fed infants or toddlers without zinc-rich complementary foods); genetically based (acrodermatitis enteropathica, acquired zinc deficiency of lactogenic origin); or acquired (secondary) deficiency in low birth weight and prematurity, gastrointestinal and hepatic disease, and cystic fibrosis [185]. Paronychia is the most common sign, associated with slow nail growth and, less commonly, leukonychia, Muehrcke’s lines, Beau’s lines, and fragility [186].

Psychiatric disorders

Anorexia nervosa and other eating disorders
See Chapter 15.

Drug-induced nail disorders
See Chapter 16.

Benign tumors
See Chapter 21.

Melanonychia and melanoma
See also Chapter 21.

Longitudinal melanonychia (Figs 10.44a–c, 10.45a–c) in children is less common than it is in adults. In ethnic origins such as Afro-Caribbean, in which all adults gradually acquire pigmented streaks in the nail, it is still rare to see it in children under the age of 10 years. In other dark-skinned ethnicities, the same pattern is seen, with an increase in the prevalence of melanonychia as a benign phenomenon with age. Longitudinal melanonychia can be light to dark brown (usually functional melanonychia) or browner (usually lentigo and nevus) with a grayish background in the former and brown to grayish in the later.

Melanonychia develops when the matrix keratinocytes are unable to disintegrate the excess of melanin in the matrix. The melanin is transferred into matrix keratinocytes that migrate obliquely upward and distally during nail plate genesis [187].

Nevi represent a manifestation of a focal mosaicism as they develop from postzygotic mutation. This means that the size of a nevus is genetically predetermined (which may be the cause of recurrence in seemingly completely excised matrix nevi). The earlier the postzygotic NRAS mutation occurs, the larger the involved area will be [188]. Among congenital nevi, some are present at birth or during the first year of life while other “congenital-type” nevi are not visible then, but emerge before the age of 5 years.

Blue nevi are rare and can present with a blue/gray or black macule or nodule under the nail, although cases demonstrating longitudinal melanonychia have been reported. The majority of presentations are in adults [189–192], although one report cites presentation at age 21 years of pathology present at birth [193].

It is not known whether lentigines and nevi exist purely in the nail bed, except one case with a pigmented nail bed lesion overlapping the matrix in a 2-year-old Japanese girl [194].

In white and less pigmented racial groups, the concern with a pigmented streak is that it may represent an early subungual melanoma. However, the likelihood of this in a child is remote, and very few cases have been reported.

Figure 10.44 Nail lentigo in a child. (a) Clinical: Narrow darkly pigmented band. (b,c) Single melanocytes in relatively low density, highlighted in a microphthalmia-associated transcription factor (MiTF) immunostain.
The majority of the published cases are based on two main histopathological characteristics: cellular atypia and architectural disorder, both being very difficult to assess in children. Nail nevi in children may display unusual histological features, including an irregular distribution of melanocytes, with some present throughout the nail matrix epithelium and even in the nail plate on occasion. This distribution can be highlighted using immunostains [195]. However, in heavily melanized lesions, which are not uncommon in children, even such staining can fail to help. Melanocytes may be of the larger pigmented epithelioid variety, and Spitz nevus with its inherently atypical melanocytes has also been reported [196–199] (Fig 10.46a–c). Nevi may involve the nail folds and nail bed and thus may be poorly circumscribed. This makes interpretation as to whether melanoma should be considered challenging. Given the rarity of bona fide cases [195, 200, 201], a high threshold for this diagnosis should be observed and conservative treatment should be enacted. In addition, no cases of invasive melanoma have been reported in children with a presentation of longitudinal melanonychia, and thus it is also possible that some of the reported cases represented instead markedly atypical nevi. Whether the criteria used in adults, which are also fraught with diagnostic difficulty and evolving understanding, can be applied to children is unknown. Perhaps only severe widespread atypia should be interpreted as melanoma and in the correct clinical setting (Fig. 10.47a–c). The latter is crucial. Nail unit melanoma that developed from a congenital nevus has not been reported so far except for Lyall's case [202] but without longitudinal melanonychia. The scarcity of nail unit melanoma explains our “wait and see” policy about longitudinal melanonychia, even if biopsy has shown a nevus. Melanonychia associated with periungual pigmentation, Hutchinson-like or micro-Hutchinson's sign, has the same significance.

Figure 10.45 Nail nevus in a child. (a) Clinical: Light brown narrow band with tan background and regular lines within it, with scar from prior biopsy. Courtesy of M. Hinshaw, MD. (b,c) Melanocytes in nests in the lower matrix, highlighted in a microphthalmia-associated transcription factor (MiTF) immunostain (which also stains superficial matrix melanocytes in a “pitfall”).
The procedure to follow longitudinal melanonychia starts with the ABCDEF rule [203], which is unfortunately of limited value for children. Dermoscopy is inescapable but is less useful than in adults (see Chapter 4).

The dermoscopic features observed in subungual melanoma show some features of acral melanoma, including the parallel ridge pattern of the pigmentation and the irregular diffuse pattern of acral pigmentation. In contrast, in newborn or prepubertal children, the periungual pigmentation in nevi reproduces the benign features of acral skin, i.e. a parallel nail furrow pattern and a less common lattice-like and fibrillar pattern that can be considered as the signature feature of congenital nail unit nevi. Unfortunately, besides the fibrillar pattern, neither the clinical features nor the dermoscopic observations of congenital nevi are specific. Moreover, the features at early stages mimic adult melanoma. Consequently, monitoring over time is of crucial importance: this will constitute the best management, because a paradoxical course of longitudinal melanonychia and/or periungual pigmentation, common enough in congenital nail unit nevi, may be observed as disappearance of longitudinal melanonychia in children, especially from Asian extraction. In one study of four Japanese children, pigmentation of the nail plate presented in each of them between the age of 1 and 24 months. Histology was not obtained in any case, and over the follow-up period of 3–11 years the pigmentation changed. In all nails, there was a process of evolution and subsequent regression, although it is not clear whether the pigment disappeared completely; the clinical pattern was termed “regressing nevoid nail melanosis in childhood” [204]. It has been said [205] that dots could be an indicator of a dermoscopic sign of regression of longitudinal melanonychia in children. However, because the lesions have not been biopsied, the clinically disappearing lesion cannot be considered with certainty as complete histological resolution, as suggested in one of our cases (Fig. 10.48a–d) [206].

![Figure 10.46 Atypical nevus and Spitz nevus in children. (a) Clinical: Narrow brown band and slightly irregular pigmented band. Courtesy of P. Rich. (b,c) Irregular distribution of melanocytes in some areas in this case but mainly in the lower epithelium with some discrete nests. Another case of Spitz nevus of the matrix, with spindled/epithelioid melanocytes in nests.](image1)

![Figure 10.47 Melanoma in situ. (a) Clinical: Near complete melanonychia with a blue-dark hue and micro-Hutchinson's sign. (b,c) A poorly circumscribed proliferation of atypical, mainly single melanocytes in elevated density throughout the nail matrix, as highlighted in a SOX-10 immunostain.](image2)
The need for matrix biopsy in childhood melanonychia is controversial [207], but if there is considerable doubt biopsy is necessary [208]. It is acknowledged that benign matrix nevi can show alarming features with a range of deep pigmentation. In dark-skinned children, Hutchinson’s sign is less easy to determine because of the common feature of pigmentation in the distal margin of the proximal nail fold of darker races. Hutchinson’s sign (Fig. 10.49), triangular melanonychia with a broader proximal than distal margin [209], multicolored appearance, nail plate erosion, and monodactylic involvement (common in the initial presentation) can all give rise to a decision to biopsy. Nevertheless, it will rarely reveal a subungual melanoma [210].

In a French series of longitudinal melanonychia in children, eight children between the ages of 2 and 14 years were reported; in these children, melanonychia had been noted at some point from birth up to 12 years of age [211]. Five had excisional biopsy of involved matrix, revealing junctional nevi. Two were left with significant

![Figure 10.48](image1.png)

(a) Longitudinal melanonychia in a 4-year-old baby. (b) Nine months later. Note the fading of the band. (c) Intraoperative onychoscopy showing pigmentation of the nail matrix and hyponychium. (d) Histology showing a typical junctional nevus.

![Figure 10.49](image2.png)

Hutchinson’s sign. Courtesy of B. Richert.
postoperative nail dystrophy. Three were followed with no biopsy and there was no clinical evolution. A similar finding was made in a larger Italian study in which histology was obtained from 100 patients with isolated longitudinal melanonychia [196]. Twenty-two of 100 lesions had histology of melanocytic nevi. Eleven of the 22 were children under the age of 14 and no alternative diagnosis was made in this age group. In two children, the pigment was noted to have faded between the initial consultation and biopsy [212]. A clinical and histopathological study of 40 cases of longitudinal melanonychia in children below 16 years of age found a lentigo in 12 children, a nevus in 19, and functional longitudinal melanonychia in nine [213].

Direct matrix dermoscopy reliably differentiates lentigines and nevi from melanoma [214]. This is now followed by intraoperative dermoscopy [215]. Reflectance confocal microscopy is a recent non-invasive method, but more studies are required regarding its utility in nail unit pigmented lesions.

The genetic approach with DNA ploidy investigations has been used to differentiate subungual nevi from melanoma, but these studies generally require more cellular lesions. Multiple gene amplification is found in subungual melanomas early in their progression, about one-half of them in the cyclin D1 locus [216]. Comparative genomic hybridization (CGH) allowed the diagnosis of subungual melanoma to be made in a 13-year-old girl [217]. CGH and fluorescence in situ hybridization have detected melanocyte aberrations in the skin adjacent to acral melanoma [218, 219].

Finally, despite the very small number of children with subungual melanoma [220–229], a brown streak in the nail, present for many years, without alteration, and which all of a sudden widens or becomes darker, must raise concern and requires excisional biopsy with at least histopathological examination. In addition, the question remains as to whether pigmented streaks with even benign histology in childhood become melanomas in adulthood. Six cases of longitudinal melanonychia in children have evolved in melanoma during adulthood, respectively at the age of 17 (Fig. 10.50), 18 (two cases), 20, 27, and 32 [230–234].

It is too early to imagine replacing our up-to-date technologies by the canine olfactory detection of melanoma-emitting characteristic patterns of volatile organic compounds [235].

**Other malignant tumors**

See Chapter 21.

**Trauma, finger sucking, and nail biting**

See also onychotillomania in Chapter 15.

**Bullous eruption of the newborn**

This bullous eruption in the newborn infant is always present from the time of birth, beginning in utero [236]. It may appear on the dorsum of the thumb or index finger.

The bullae measure from 0.5 to 15 cm in diameter. The fluid is clear, light yellow, and sterile. These lesions are presumed to be self-inflicted (in utero) as a consequence of a vigorous sucking reflex in otherwise normal newborns. However, there is a risk that more serious diagnoses will be overlooked if this conclusion is drawn too lightly.

The differential diagnosis [236] includes epidermolysis bullosa (Figs 10.51, 10.52), incontinentia pigmenti, pemphigoid gestationis affecting the newborn, neonatal erythema multiforme, and bullous congenital ichthyosiform erythroderma as well as infective causes. Congenital syphilis is very rare and staphylococcal, streptococcal, or herpetic bullae generally do not occur before the fifth day of life. Most of these eruptions would normally be more widespread than the nail folds. However, generalized blistering disease can sometimes present with both nail fold blisters and nail shedding due to loss of adherence with the periungual tissues.

In all forms of epidermolysis bullosa affecting the nails, recurrent bullae may result in nail thinning, pterygium formation, and aplasia. Sometimes the nails become thickened and onychogryphotic. Meticulous hygiene, topical antibiotics (mupirocin), and synthetic dressings may optimize nail regrowth when possible. In these patients shoes with wide toe boxes can also be used to minimize the loss of toenails from friction.

Figure 10.50 Benign histology in childhood has become melanoma in adulthood. Courtesy of R. Nakamura.
Nail Disorders in Childhood

Epidermolysis bullosa
See Chapter 9.

Finger sucking, nail biting, and habit tic

Finger sucking (Fig. 10.53) is usually limited to those under the age of 5 and is a normal childhood activity. It only occasionally gives rise to secondary nail changes such as onycholysis [237] or problems such as the mother’s false nail implanting in the hard palate when sucking her finger as a nipple substitute [238]. After that age, opinion is not clear as to whether it represents a problem in terms of oral development, with the potential risk of altering the bite of the incisors [239] such that they do not meet in the front. Atypical patterns of finger sucking have resulted in deformity of the digits, requiring surgical correction [240]. Transfer of infection from
finger to mouth and possible systemic illness are potential risks at all ages [241]. It is seldom necessary to pursue a specific strategy to persuade a child to stop sucking their digit, but such strategies exist [242] and may be valuable when faced with intractable paronychia or relevant dental problems. Allergic reactions to specific nail varnish resins designed to discourage biting have been reported [243].

Nail biting (Fig. 10.54a,b) is a more complicated habit with direct connotations of self-harm. In spite of this, it is common. A study in primary and secondary schools in the north of England revealed that 36% of children aged 5 bit their nails, rising to 57% at age 12 and falling to 31% by 16 [244]. The pattern and extent of biting rarely take the form of onychotillomania seen in adults, where the entire nail plate may be lost and psychiatric problems may be manifest [245–247]. Simple nail biting appears unrelated to psychiatric illness [248], although some studies have proposed that the behavior is associated with significant stresses and anxiety [249]. Turning the interpretation around, 31% of children with trichotillomania are also nail biters [250].

In addition to predisposing to periungual infection and chronic paronychia, nail biting can result in soft tissue problems in the mouth. Fragments of nail can get caught between teeth or embedded in periodontal soft tissues, provoking gingivitis. This reaction is difficult to settle unless the fragment is dislodged or there is abscess formation and liquefaction of local soft tissues [251, 252].

A study performed via orthodontic practitioners claimed that nail biters between the ages of 13 and 15 were at greater risk of tooth root resorption than non-nail biters [253]. The explanation for this was that long-term repetitive biting seen in other circumstances causes root resorption and nail biting is likely to do likewise. Although this finding was determined through jaw radiographs, it is not clear to what extent it would have a clinical correlate in terms of oral health.

Other forms of nail trauma seen in adults are also occasionally seen in children. There is a single report of “washboard nails” in an 11-year-old girl. She admitted to the habit of rubbing and picking at the thumb cuticle from the age of 5 years. The nail consequently developed a series of irregular transverse depressions associated with loss of cuticle and slight bolstering of the proximal nail fold [254]. Longitudinal melanonychia or diffuse nail pigmentation, even associated with non-melanoma Hutchinson’s sign, can be observed [255–257].

**Nail degloving**

Nail degloving refers to partial or total avulsion of the nail and surrounding tissue.
This new syndrome was described by Baran and Perrin in 2008 [258]. Typically, it appears as a thimble-shaped nail shedding or a partial or total loss of the nail organ with soft tissue. Nail degloving represents the ultimate stage of a faulty attachment of the nail apparatus to the distal digit resulting from trauma, drug reactions, and dermatological diseases.

1) Trauma (the etiology of trauma is well known and may be found at any age).
2) Iatrogenic reaction (drug-induced conditions are rare).
3) Epidermolysis bullosa (nail degloving has been observed in autosomal dominant epidermolysis bullosa (Fig. 10.55).
4) Kawasaki disease [259] (Fig. 10.56) A progressive extrusion of the entire nail apparatus was limited to the finger and occurred after 7 weeks and lasted for 15 days. Regrowth of normal nail was obtained after 3 months.
5) Gangrenous conditions (the occurrence of acute peripheral gangrene in newborns is a rare emergency event). A few hours after delivery the newborn develops blisters on the digits. Gangrene appears the following day. The differential diagnosis includes metabolic diseases, vasculitis, vascular malformation, and “congenital erosive vesicular dermatosis with reticulated supple scarring” [260].

Infantile ingrown toenails

Infantile ingrown toenails present with several variants. The age distribution shows two peaks: 0–3 years old and 9–13 years old. Ingrown nails develop in different patterns at different ages. Conservative measures are always suggested. Also, they are best combined with educating the family as it is essential to avoid constricting clothes. The use of an antiseptic shaving soap under the occlusion is certainly helpful, as well as a cotton wool or wound closure strip insert. Finally, appropriate nail care is essential. The multiple anchor-taping method for the ingrowing nail is also a useful method for appropriate nail care.

The etiology of infantile ingrown toenail may have a congenital origin: intrauterine positioning, inherited factors, and normal variations in the development of the great toe.

However, acquired factors may also play a role: prone position, constricting garments, unsuitable shoes, and improper nail care.

There are six types of ingrown toenail in infancy:

1) congenital malalignment of the great toenail
2) congenital hypertrophic lip of the hallux
3) grasp reflex multiple ingrown fingernails
4) distal embedding with normally directed nails (see Chapter 22)
5) distal lateral embedding (see Chapter 22)
6) overcurvature of the nails (see Chapter 22)
7) retronychia (see Chapter 22).

Congenital malalignment of the great toenail

In 1978, Samman [261] described several cases of a “dystrophy” limited to one or both great toenails. Baran et al. [262] termed this “congenital malalignment of the big toenail” (Fig. 10.57a,b), placing the emphasis on the main characteristic of this condition: the nail plate is deviated laterally with respect to the longitudinal axis of the distal phalanx. Medial deviation is rare, but possible [263].
Transverse ridging, which may be single or more often multiple, is one of the earliest signs to appear and may develop over the entire surface of the nail plate [264]. The ridges form regular waves when they are numerous. They seem to follow recurrent episodes of damage to the matrix, sometimes leading to latent onychomadesis or shedding of a large portion of the nail; the new nail is already well advanced before the old is lost.

The nail plate may be thickened with gradual tapering of the distal portion. Sometimes there is associated onycholysis, and the nail may acquire a grayish tint, a brown discoloration (due to a hemorrhage), or a greenish hue (which is due to *Pseudomonas*). This would be of minor importance if it were not for the complications that may arise both in infancy as ingrowing toenail [265], even congenitally [266], as well as in the elderly (hemionychogryphosis).

The most important complication is ingrowing toenail with painful inflammation of part of the perionychial area. At this stage, examination may show a nail which is short, pressing against a rim of skin at the extreme tip of the great toe and forming a lip. Primary malalignment of the nail appears then to be the main factor causing the “nail embedding.” Because the main direction of nail growth in these patients occurs laterally, there is insufficient forward thrust to allow the nail plate to mount the heaped-up tissue in front of it, even when physiological koilonychia exists [262, 264, 265]. At this stage, a simple surgical procedure successfully realigns the whole nail apparatus (Fig. 10.58). The best results are obtained when the malalignment is corrected surgically before the age of 2 years [267, 268], but we have obtained good results even in adulthood. Spontaneous improvement [263, 268, 269] or even complete resolution occur in less than 50% of patients under 10 years of age. Careful examination of the posterolateral corner of the affected nails may reveal a bulge in some; therefore, we postulate that it could result from traction upon the nail plate by the thickened dorsal expansion of the lateral ligament at the distal interphalangeal joint described by Guéro et al. [270] and demonstrated on magnetic resonance imaging.

Management must depend on accurate assessment of the degree of malalignment and the associated changes [271], since it appears impossible to foresee spontaneous realignment [272].

- If the nail deviation is mild, and in the absence of complications, the nail, as it hardens, may overcome the initial slight distal embedding, and sufficient normal nail may grow to the tip of the digit to prevent further secondary traumatic changes. Treatment should be conservative.

  If the deviation is marked and the nail is buried in the soft tissues, the patient may be disabled later on, in childhood and in adult life. Should an operation be chosen, a crescent wedge-shaped resection must be carried back proximal to and below the nail bed and nail matrix associated with the simple section of the dorsal expansion of the lateral ligament. The crescent has to be larger on the medial than on the lateral aspect. A small, triangular area is also excised at the start of the lateral incision line, thereby enabling the whole nail apparatus to be swung over the resected area so that it can be realigned and then sutured. When the nail deviation is medial instead of lateral, in contrast to the usual type, the crescent has to be larger on the lateral aspect than on the medial one, and a small triangular area is also excised at the start of the medial incision line, thereby enabling the whole nail apparatus to be swung over the resected area, so that it can be realigned and then sutured [265].

- Surgical rotation of the misdirected matrix, usually associated with the simple section of the dorsal expansion of the lateral ligament [272].

---

*(Figure 10.57 (a) Bilateral congenital malalignment of the great toenail. (b) Unilateral congenital malalignment.)*
● Congenital malalignment of the great toenail is an inherited condition [273, 274] and the “inherited nail dystrophy principally affecting the great toenails over 3 generations” [275] pertains to the same dysplasia. Sometimes, this condition may be associated with tibial deviation of the second toenail.

**Congenital hypertrophic lip of the hallux**

When they appear at birth, hypertrophic lateral nail folds are generally bilateral and symmetrical, affecting most often the medial nail fold of the hallux (Fig. 10.59a,b). They present as firm, red, tender swelling [276]. They enlarge progressively, sometimes covering one-third of the nail plate [277]. They may be the result of asynchronism between the growth of the soft tissue and the nail. The hypertrophic lateral lip grows faster than the nail plate, leading to ingrowing, with pain, which increases when walking begins [278]. This condition, which resembles recurring digital fibrous tumor of childhood, usually disappears spontaneously after several months.
Grasp reflex multiple ingrown fingernails

There is a new clinical entity of the ingrown fingernails of infants being associated with the grasp reflex, inducing paronychia. Twenty-six cases were published and the median age was 1 month (age range 6 days to 4 months) [279]. Since ossification of the distal phalanx has not developed in infants, the nail plate can easily penetrate into the surrounding soft tissue, under pressure [279]. Because the grasp reflex causes pressure on the fingernail due to a foreign body to the buried nail, the soft tissue swells and encourages the condition of ingrowing nails.

A grasp reflex may be elicited by the stimulation of the palm of the hand by firm pressure to produce flexion of the fingers. It usually disappears by about 3 months of age. Although in severe cases the administration of antibiotics or drainage was needed to treat abscess formation around the nail plate, the mild cases have a good prognosis with the advice to reduce stresses on the fingernail.

References

Nail Disorders in Childhood


Nail Disorders in Childhood


Introduction

The elderly constitute a large and rapidly growing segment of the population [1]. Nail disorders are frequent among the geriatric population. This is due in part to the impaired circulation, the susceptibility of the nail to fungal infections, faulty biomechanics, neoplasms, concurrent dermatological or systemic diseases, and related treatments [2]. Alterations differ on the fingernails from those on the toenails. Those on the fingernails are mostly cosmetic, whereas onychial disorders on the foot are a major complaint in the older population. The toenails are more significantly affected by aging as a result of the anatomical location, the forces of continuing activity, and environmental factors associated with lifelong ambulation and footwear [3]. Changes in the hand are more related to diminished tissue repair and inflammatory or degenerative changes of the distal interphalangeal joint [4].

A study on 1000 individuals older than 65 years, who were ambulatory and not institutionalized, revealed that 75% of all patients complained of pain, 57% were receiving current care for diabetes, 82% had signs of peripheral vascular disease, 65% had one or more foot deformities, 60% demonstrated loss of protective sensation, and 94% had onychodystrophy [5]. A Korean study on 180 subjects revealed that all of them had at least one kind of foot problem and that the most prevalent one was nail problems [6]. Another study performed in India showed that 98 patients out of 100 exhibited at least one change due to aging [7].

Foot pain affects 20–30% of community-dwelling older people and is associated with decreased ability to perform activities of daily living, problems with balance and gait, and increased risk of falls [8]. Foot problems in the elderly, especially the nails, are prevalent and the geriatric foot is expected to emerge as one of the most important problems in the geriatric field [6]. The ability to walk requires a catalyst – foot health [9]. Keeping patients walking is a goal for future aging generations.

Geriatric patients usually complain about the inability to cut their thick, hard toenails. This simple problem can be magnified by poor eyesight, paresthesia, and inability to bend and reach their feet [10]. Trembling and inadequate tools add difficulty. Adequate care of legs and feet in the elderly are associated with poor choices in footwear, structural changes brought on by aging, and inadequate knowledge about prevention and treatment [11].

Nail changes are common in the elderly, and family physicians are best placed to diagnose and treat these. It is important that family physicians also recognize less common but more serious nail problems that require immediate treatment [12].
Chapter 11

Modifications of the morphology and composition of the nail

Contour modification

With age, the nail may acquire a different shape: the nail may flatten (platyonychia), become concave (koilonychia), often as the result of thinning of the nail (Fig. 11.1), or become convex (clubbing), as observed in chronic bronchopulmonary diseases. On the toenails, thickening of the nail plate is most commonly associated with a proximal to distal increase of the transverse curvature (pincer nail) (Fig. 11.2). This deformity arises from an enlarged base of the distal phalanx to which the matrix is firmly bound. As a result, the curvature of the proximal (matrical) nail plate portion will decrease (flatten) and consequently the curvature will increase distally, progressively pinching the distal nail bed [13, 14]. Conservative treatment is often proposed when the condition starts to be painful, as older patients fear surgical procedures on the toenails. A variant of the nail brace technique has been shown to be effective in reducing the transverse curvature of the nail. Relief of pain can be achieved in almost 100% of cases in a 3-month period. Widening of overcurvature of the nail occurred in all cases and was demonstrated by measurement of plaster molds [15]. However, removal of the device is followed by an immediate recurrence [14]. Surgical treatment immediately alleviates the pain from the pinching of the distal nail bed (see Chapter 22).

Color modification

The color of the nails of aging individuals modifies over time. The shade varies from white to yellow or even to gray. The nails become opaque and dull [16]. The lunula is decreased in size or even absent [17]. The most common age-related nail change was a pale, dull, and lusterless appearance of the nails in 73% of patients (Fig. 11.3) [7]. In a large study on 512 inpatients, the so-called Terry's nails were found in 25%. The authors confirmed Terry's finding that the abnormality was associated with cirrhosis and demonstrated associations with chronic congestive heart failure, adult-onset diabetes mellitus, and age. A modification in color that has been termed "Neapolitan nail" has been associated with aging, as the succession of a white proximal portion, a normal pink central band, and an opaque free edge suggested a slice of Neapolitan ice cream (Fig. 11.4) [18, 19].

Acral arteriolar ectasia is a distinct vascular malformation consisting of purple serpiginous vessels on the dorsa of the digits, first arising in the fifth decade of life. The vessels are ectatic arterioles and are believed to represent a rare vascular malformation [20].
Linear nail growth modifications

Orentreich and Sharp [21] demonstrated that linear thumbnail growth decreases on average by 38% between the third and ninth decades. In their study, the decrease in growth in women was greater up to the sixth decade; thereafter no change was observed until the eighth decade. In men, the slowing was more pronounced from the sixth to the eighth decades. Orentreich et al. [22] also claimed that determination of the linear nail growth may demonstrate physiological aging. Some authors have measured their own nail growth rate over time. Bean [23] noted that the average linear growth of his left thumbnail decreased from 0.123 mm/day at 32 years old to 0.0095 mm/day at age 67. Dawber recorded a 10% drop in his right index linear growth over a 12-year period [24]. Rao [25] found prominent/increased ridges in 85% of his series with no significant difference between the percentages of fingers and toenails involved. Singh et al. [2] estimated that nail growth decreases by approximately 0.5% per year between the ages of 20 and 100 years. This may be considered an excellent evolutionary response as some older individuals experience problems cutting their finger and toenails due to poorer eyesight and reduced manual dexterity and flexibility needed to groom one’s nails, especially the toenails [26]. Besides atherosclerosis, other factors may intervene in the decline of the linear nail growth, such as impaired vascularization, nutritional deficiencies, and hormonal changes (see Chapter 1).

Consistency and thickness modification

Fingernails tend to soften and weaken with age whereas toenails thicken and harden [27]. Older patients, mostly women, often complain of nail fragility: their fingernails are soft, split easily into layers, and break longitudinally. The latter may result from the exaggeration of the longitudinal ridges: the nail breaks at the junction between the thick ridge and the thinner part of the nail plate. Several studies have demonstrated that brittle nails and prominent longitudinal ridges were the second most common nail changes in the elderly after the modification of color (Fig. 11.5) [25, 28]. Treatment is difficult, not to say illusory in most cases. Patients should wear plastic gloves over light cotton glove linings for all house care, including peeling of vegetables or fruit. Most patients are reluctant to do this. Nail hardeners may also be suggested: either a modified nail varnish that functions as a base coat or a hardener, such as 3–5% formaldehyde or dimethyl urea, which overcomes the objections related to formaldehyde [29]. Oral biotin has shown some interesting results [30, 31].

Histological modifications

Senile changes are thought to result from impaired peripheral circulation, commonly due to atherosclerosis, even in the absence of occlusion of the vessel lumen. A histological study revealed minimal thickening of the walls of the blood vessels in the nail generative areas. In the nail bed, there is thickening of the blood vessels and degeneration of elastic tissue. These alterations were more prominent and more diffuse than they were in the adjacent, glabrous perionychial skin. The change in the elastic tissue, present to a lesser degree beneath the lunula, is absent from the dermis of the matrix, which is covered by the proximal nail fold [32]. The nail plate contains an increased number of “pertinax bodies” (remnant of the keratinocyte nucleus) (Fig. 11.6) compared with the normal adult nail. These may be interpreted as remnants of keratinocyte nuclei. Retarded nail growth results in larger corneocytes [33]. In contrast to what is noted in young adults, there is a discrepancy and an irregularity in
the turnover of the matrix cells. These variations are probably responsible for the exaggeration of the longitudinal ridges observed on senile nails (Fig. 11.5) [34]. Nail bed capillaries show frequent distortions in normal individuals over 70 years of age, especially numerous and tortuous capillary loops.

Chemical content modification

The nail plate’s chemical composition is also altered, with an increase in carbon and a decrease in nitrogen contents with aging [35]. While there is no significant change in the total lipid content, the proportions of the different lipid fractions making up the total lipid content become more variable with advancing age [36]. Fingernail and toenail calcium concentrations decrease with age in both men and women, whereas magnesium concentrations tend to increase. Postmenopausal women have lower fingernail calcium concentrations than premenopausal women. Lumbar bone mineral density shows a significant positive correlation with fingernail calcium content. The measurement of fingernail calcium content may be useful as a predictor of osteoporosis [37].

Fungal infection of the nail

Onychomycosis is reported to be more prevalent in the elderly. This may be attributed to reduced peripheral circulation, slower growth of nails, inactivity, suboptimal immune status, diabetes, larger distorted nail surfaces, difficulty in grooming the nails and maintaining foot hygiene, frequent nail injury, and increased exposure to disease-causing fungi [38–40]. A survey in Ohio, USA, showed that approximately 14% of the general population had fungal nail infection. In people over 70 years, the rate reached up to 50% [41, 42]. This increased prevalence seems to lessen over 80 years [41, 43]. Onychomycosis in residents of long-stay institutions may vary from 37% [44] to 64% [45] according to different studies. As in the general population [46], there is still a male predominance in the elderly [47, 48], and the most common presentation is the distal and lateral subungual onychomycosis mostly affecting the great toenail (Fig. 11.7).

White superficial onychomycosis is the second most common presentation and generally involves the third and/or fourth toenails [47]. Long evolution leads to total dystrophic onychomycosis. It may be associated with such a thickened nail that it may impair footwear and gait and may contribute to reduced mobility [49]. Pressure from the dystrophic thick nail may result in torpid ulceration, especially when accompanied by peripheral vascular insufficiency.

Onychomycosis is mostly due, as in the general population, to dermatophytes [48], especially *Trichophyton rubrum* and *Trichophyton mentagrophytes* [47]. A study demonstrated that there is no difference between the etiology of the institutionalized elderly onychomycosis from that reported for the general population [50]. In elderly patients with trophic disorders of the legs, repeated isolation of *Candida ciferrii* from toenails was reported [51]. *Onychocola canadensis*, often involving all the toenails, with a yellowish, slightly hyperkeratotic, and markedly friable dystrophy, is probably also underestimated as an agent of onychomycosis in elderly individuals [52, 53] with arteriovenous problems associated with leg ulcers, because of the slow growth of the fungus in culture and the necessity for a subculture for identification [54].

Approximately 34% of people with diabetes have onychomycosis [55] and the rate increases with age and male gender [48, 56]. In India, the risk of developing onychomycosis is considered to be three times greater in
The Aging Nail and Related Disorders

those with diabetes than in those without [57]. T. rubrum is the prevailing pathogen [55]. Patients with diabetes have increased difficulty in performing regular foot check-ups because of obesity and complications of diabetes such as retinopathy or cataracts [58]. Diseased thickened nails, poorly trimmed with sharp edges, can injure the surrounding soft tissues; excessive pressure on the nail bed may result in ulcers that may go unnoticed because of the sensory neuropathy. These may act as an entry point for bacteria or fungi with limb-threatening complications, leading to possible amputation [42].

Patients with peripheral vascular disease have a prevalence of onychomycosis of 36%, very similar to those with diabetes. T. rubrum remains the most common pathogen [59, 60]. Impaired perfusion of the lower extremities results in suboptimal oxygenation and reduced metabolic exchanges of nutrients and other substances in the foot. This may instigate and spread onychomycosis, delay or hinder clearance of the disease, and expose the patient to reinfection [61, 62]. A study evaluated the predisposition effect of venous insufficiency and peripheral arterial disease on toenail onychomycosis. It demonstrated a significant relationship between onychomycosis and venous insufficiency, but not with peripheral arterial disease [63].

Elderly patients have specific risk factors for poor response to therapy for onychomycosis, including frequent nail dystrophy, slow growth of nails, and increased prevalence of peripheral vascular disease and diabetes mellitus. In this type of patient, treatment must be individualized and will depend on the patient’s needs, his/her physical condition, the location of the onychomycosis (finger or toes), the existence of any associated pathology, the type of onychomycosis, the existence of an underlying vascular impairment, and the daily medication intake. Drug interactions are highly probable in the elderly, especially with the azoles. Misunderstanding and communication problems may increase the risk [64]. A patient in good health can be treated in the same manner as a young adult. Thickened toenails may require less medication but more chiropody. This may involve the abrasion of hyperkeratotic nails by means of a specially designed electric drill [65]. Combination with local treatment may be an option in people with diabetes [66]. If possible, systemic treatment should be avoided in patients taking several medications to avoid possible drug interactions.

Terbinafine is the drug of choice for dermatophyte onychomycosis, with greater mycological cure rates, less serious and fewer drug interactions, and a lower cost than continuous itraconazole therapy [67]. Another option is a single weekly dose of fluconazole (300 mg) or terbinafine 250 mg daily for 1 week every month [68]. Both continuous terbinafine and itraconazole pulse therapy have been shown to be effective and safe in the management of dermatophyte toenail onychomycosis in people with diabetes [69]. Adjunct debridement may improve the clinical and complete cure rates compared with terbinafine alone [70, 71]. Chemical nail avulsion, which carries no risk to the ischemic toe, in association with antifungal nail lacquer is favored by some authors [72, 73].

In general, the topical nail lacquers amorolfine and ciclopirox are not practical for elderly patients because of the recommended frequency of application, periodic routine debridement of affected nails, long duration of therapy, and difficulty in reaching their toenails (often requiring the assistance of a third person to apply the treatment properly) [38].

Iatrogenic nail changes

Drug-induced nail disorders should always be suspected in an older patient taking many medications. As many drugs may not be withdrawn, it might be difficult to attribute the responsibility for the nail alteration to the drug. However, some well-known side-effects should be remembered, such as longitudinal melanonychia from hydroxyurea, digital necrosis from β-blockers (propranolol), captopril-induced onycholysis, hematomas from anticoagulants and others (see Chapter 16).

Benign tumors

The myxoid pseudocyst, which is a leak of joint fluid secondary to laxity of the capsule because of osteoarthritis, is the most common benign tumor observed in the elderly. There is a female predominance. It mostly affects the first three fingers; location on the toes is possible but unusual. When located over the matrix, the cyst is responsible for a longitudinal groove (see also Chapter 21) (Fig. 11.8). If the lesion is not embarrassing the patient, abstention is the rule. Otherwise, repeated puncture with compressive dressings for several weeks or months may be an option. For willing patients without contraindications, surgery with ligation of the pedicle after injection of methylene blue into the joint is the best treatment [74] (see also Chapter 22).

Malignant tumors

Epidermoid carcinoma of the nail apparatus may be observed at all ages but has a peak between 50 and 69 years. It is mainly located on the first three fingers. Toes are very rarely involved [75]. It has been demonstrated that about 60% of all epidermoid carcinomas are related
to a previous oncogenic human papillomavirus genital infection [76]. It presents in many guises and is a great mimicker at the nail apparatus (see also Chapter 21). One should always bear it in mind when considering any long-lasting nail dystrophy (Fig. 11.9). Biopsy is mandatory. This tumor is not very aggressive, with a metastatic rate of only 3–5% when invasive. The in situ form, called Bowen disease, has an excellent prognosis. Surgery should be conservative as long as there is no bone involvement proven on radiographs or on histology [75] (see also Chapter 22).

Melanoma of the nail apparatus affects predominantly women around 65 years old, on the great toenail in more than half of the cases, followed by the thumb and little finger (Fig. 11.10) [74]. Any suspicious longitudinal melanonychia or lesion evoking a pyogenic granuloma should be investigated immediately. Amputation is no more the rule; the Breslow index guides the management [77–80] (see also Chapter 22).

Figure 11.8 Pseudomyxoid cyst. The constant pressure on the underlying matrix is responsible for the longitudinal groove.

Figure 11.9 Bowen disease. This long-lasting lesion was thought to be a wart and was treated as such. Eventually, complete ablation of the nail apparatus was necessary.

Figure 11.10 (a) Melanoma, nodular type on the third toenail. This was interpreted as trauma for several months before the correct diagnosis was made. (b) Melanoma of the fifth toenail. Hidden by the overlapping of toes in a patient with Alzheimer disease. Note the periungual spreading of the pigmentation (Hutchinson’s sign).
Trauma from footwear and pedal deformities

Nail changes due to footwear and added pedal deformities

More than 80% of women aged over 65 complain of foot pain [81]. Women outnumber men up to 13 times in chronic foot disorders [82]. Such a female predominance results from routinely wearing ill-fitting shoes (pointed shoes with heels). What can be worse than a square forefoot in a triangular space [83]? Osteoarthritis, more prominent in women after menopause, may also intervene in the pathogenesis of foot and toe deformities with subsequent toenail alterations. The latter are aggravated by arterial deficiency. The bodyweight, often also increasing with age, adds its detrimental effect by increasing the interaction between toe and shoe. In men, half of the bodyweight rests on the heels. In women wearing heels, the bodyweight is transmitted to the forefoot, proportionally to the height of the heels: the higher the heels, the more distal the location of the bodyweight [84]. Faulty biomechanics such as hallux valgus, erectus, and rigidus, hammer toes and over- and underlapping toes complete the picture [85–87].

The repeated constraints between shoes and toes are mostly responsible for hyperkeratosis of the plate itself (onychauxis or pachyonychia) or of the nail bed (subungual hyperkeratosis) or even of both structures simultaneously. They arise in the areas where friction is prominent, meaning the great toenail and the fifth toe [84]. The so-called heloma or onychoclavus is a small horn of the median distal bed of the great toenail, very painful from the compression it induces between the nail and the bone (Fig. 11.11a). The onycholysis that it generates allows clipping of the detached nail to expose the whole lesion (Fig. 11.11b). It may appear black from intracorneal hemorrhages. This procedure immediately alleviates the pain, as pressure on the bed/bone has been released. Lateral examination of the foot almost always reveals a hallux erectus. Treatment is gentle curettage of the lesion. In some instances, when the horn is very deeply anchored, surgical excision in a longitudinal ellipse is recommended. Podiatric measures are mandatory to suppress the erectus with adequate functional orthotic devices. The dorsiflexed great toe associated with hallux erectus will increase rubbing against the roof of the shoe with subsequent median onycholysis or subungual hyperkeratosis; this occurs mostly when the toe box is not deep enough, a common trait of women’s shoes [86]. In hammer toes, the contracted lesser toes will induce a hyperkeratosis of the hyponychium from the rubbing against the sole. This deformity is often associated with a thickening of the distal nail plate.

Onychophosis is the hyperkeratosis of the lateral folds from repeated rubbing against the shoe and/or the adjacent toenail (Fig. 11.12) [87]. Pressure from the adjacent toe may induce a hypertrophic nail fold, also called a hypertrophic lip, asymptomatic in most instances, but that may hasten an ingrowing toenail from inadequate nail clipping. A painful horn, filling the lateral sulcus of a rotated fifth toe, may be observed in some patients: the toe is oriented in such a way that the patient ambulates on the lateral part of the fifth toenail [85].

Distal and lateral onycholysis of the great toenail is very common in the elderly and results from an overlapping of the second toe on the first one [88], promoted by hallux valgus, the so-called Morton toe (a second toe longer than the great toe), and compression from ill-fitting footwear. This detachment of the plate from its bed occurs in an area of physiological weak adherence [89]. Osteoarthritis with enlargement of the base of the

Figure 11.11 (a) Painful onychoclavus in the distal median part of the nail appearing as a blackish spot. Of course, the onychomycosis is not responsible for the onychalgia. (b) Clipping of the onycholytic zone exposes the lesion.
distal phalanx is responsible for pincer nail [14]. Permanent pressure from the second toe on the lateral side of the great toenail may account for the rise of an ingrowing nail and pain associated with pincer nail [90].

Treatment of such dystrophies should be appropriate in order to allow patients to ambulate with greater efficiency and minimal pain, thus keeping their independence. But most of the faulty biomechanics of the forefoot, as well as their consequences on the nail apparatus, are irreversible. Treatment must therefore be conservative in most instances. Moreover, when the conditions can be surgically corrected, the patient may not be a candidate for surgery owing to associated systemic diseases or concomitant therapy such as anticoagulants. Podiatric care is then the best approach to help the patient.

First, education on proper footwear, with an extra deep toe box [91], is a must. Drilling with an electric drill or a burr is helpful in most types of hyperkeratosis. If such a treatment is contraindicated (diabetes, atherosclerosis, etc.), partial or complete removal of the nail plate may be achieved with urea paste under occlusive dressings for several days, completed by mechanical debridement with a dual-action nail nipper. The procedure may be repeated as many times as necessary to ensure comfortable footwear for the patient. For skin thickening of the soft tissues such as onychophosis, debriding with a sterile new blade, avoiding any bleeding, is the initial treatment. Maintenance is provided with daily application, when feasible, of 30–50% urea paste on callosities.

Silicon prostheses and orthotic devices are the most accurate techniques in dealing with pedal dystrophies in the elderly. They reduce or cancel friction and rubbing from the shoe or from toe-to-toe interaction [90]. These devices are available over the counter in drugstores but customized ones are better as they are fully adapted to the shape of the patient’s foot: they can either protect a painful frictional area or correct the toe deformity (Fig. 11.13) [92]. Surgical avulsion with chemical cauterization of the whole (e.g. pachyonychia) or partial (e.g. pincer nail) matrix may be an option for definitive treatment. It has been demonstrated that phenol and sodium hydroxide cauteries are safe in patients with diabetes [93–95].

Nail dystrophy from inadequate nail care

Because of immobility, poor eyesight, difficulty reaching the toes due to overweight or rigidified spine, self-neglect, or even insufficient nursing service, the nails may not be trimmed for several months or years, giving rise to major distorted nails called onychogryphosis, evoking an oyster shell or a ram’s horn. The plate is very thick, uneven, yellow brown, and opaque. With pressure from footwear, the nail growth direction is pushed laterally towards the other toes or sometimes backwards (Fig. 11.14). The extremity of the nail may injure the soft tissues of the adjacent toes. This may be a cause of chronic ulceration or even gangrene, especially in patients with poor blood supply. Incorrect cutting of the nail, caused by trembling and inadequate tools, associated with pressure from ill-fitting shoes may precipitate ingrowing toenail. In the elderly patient with decreased sensation secondary to diabetes or peripheral vascular disease, ingrowing toenail can be a devastating problem with significant morbidity as they are unaware of the problem because of their neuropathy. This may lead to serious complications such as osteomyelitis or gangrene [87]. Treatment may be conservative or surgical (see “Nail changes due to footwear and added pedal deformities,” and Chapter 20).
The Aging Nail and Related Disorders

References


Figure 11.14 (a,b) Onychogryphosis. This results from poor nail trimming due to insufficient nursing service.


59. Gupta AK, Gupta MA, Summerbell RC et al. (2000). The epidemiology of onychomycosis: possible role of...


Part V

Nail Infections

Chapter 12

Fungal (Onychomycosis) and Other Infections Involving the Nail Apparatus

Roderick J. Hay¹, Boni Elewski², Bianca Maria Piraccini³, Nikki Sullivan⁴, Casey Wang², and Robert Baran⁵

¹ King’s College London, London, UK
² Department of Dermatology, The University of Alabama at Birmingham, Birmingham, AL, USA
³ Dermatology, Department of Experimental, Diagnostic and Speciality Medicine, University of Bologna, Bologna, Italy
⁴ Department of Dermatology, University of Michigan, Ann Arbor, MI, USA
⁵ Hon. Pr. of the University of Franche-Comté; Nail Disease Centre, Cannes, France

Introduction

In this chapter fungal nail infection or onychomycosis is considered in detail, together with a variety of infections occasionally seen in and around the nail apparatus; some infections are discussed, where appropriate, in other chapters (see list at end of text).

Onychomycoses occur throughout the world but there are regional differences in incidence. Precise data as to their prevalence have only recently become available and the results vary from country to country [1]. The results also vary with the method of calculation of prevalence. For instance, Roberts [2] found that, if a photographic identification method is used in randomly selected individuals, about 2.7% of subjects in the UK had changes in their nails compatible with onychomycosis. However, larger numbers have been found by direct examination of populations attending dermatologists or general practitioners. For instance, the Achilles study in Europe showed an overall prevalence of onychomycosis of 23%; it also highlighted the fact that prevalence rises above the age of 60 [3].

These estimated figures reflect substantial differences in the methods of assessing the presence of disease and the populations surveyed but the overall pattern is that of a higher prevalence of onychomycosis in temperate climates. Specific groups such as people with diabetes have also been found to have a higher prevalence than normal individuals [4]. Sociocultural and occupational factors play an important part in the increased prevalence over the past 60 years as well as the spread of organisms such as Trichophyton rubrum. In tropical areas the prevalence of onychomycosis is lower. In rural areas in Zaire,
Chapter 12

350

the incidence was found to be 0.89%, whereas in city dwellers it was 4% in men and 2.8% in women [5]. Fungal infections of the nails have been reported in 6.5–27% of miners [6]. Some 1.5% of all patients attending dermatological centers have onychomycosis [7]. Between 18% and 40% of all nail disorders are onychomycoses [8, 9] and 30% of all dermatomycoses are nail infections [10].

ONYCHOMYCOSIS

Roderick J. Hay, Bianca Maria Piraccini, and Robert Baran

Fungal infections of the nail apparatus may be classified according to the pattern of invasion of the nail apparatus (Fig. 12.1). The classification of nail disease used in this chapter is the revised scheme described in 2011 (Box 12.1) [11].

This expands on previous classification schemes to include mycoses involving the whole nail apparatus as well as mixed pattern onychomycosis. The visual appearance of the nail and accompanying lesions may provide clues to the likely identity of the infecting organism, although it is seldom possible to identify the species on clinical grounds alone. For instance, irrespective of right or left handedness, unilateral hand involvement is a common feature of dermatophytosis caused by *T. rubrum*; in such patients, both feet are commonly infected [12] (Fig. 12.2). Similarly, onychomycosis confined to the fingernails is more suggestive of a *Candida* infection, especially in those with paronychia and onycholysis, although infections caused by either *Neoscytalidium dimidiatum* or *N. hyalinum* may both produce similar nail lesions. Schemes for clinical diagnosis of onychomycosis based on the association between skin abnormalities such as scaling on the sole or between the toes that suggest fungal infection as well as nail dystrophy [13] have been described and validated.

### Box 12.1 Classification of onychomycosis

- Distal and lateral subungual onychomycosis
- Superficial onychomycosis (white or black):
  - Patchy or transverse
  - Originating from beneath the proximal nail fold, e.g. patchy or transverse
  - With deep penetration
- Endonyx onychomycosis
- Proximal subungual onychomycosis:
  - Patchy
  - Striate (transverse or longitudinal)
- Mixed onychomycosis: examples include the above patterns on the same nail
- Totally dystrophic onychomycosis
- Secondary onychomycosis
- Paronychia associated with fungi
  - Paronychium without nail plate involvement
  - Paronychium with nail plate involvement, usually proximal subungual onychomycosis

Ultimately, though, accurate diagnosis still depends on the laboratory identification of the fungus by cultural or molecular methods. Invasive onychomycosis can also be established convincingly by use of histology and appropriate stains such as periodic acid-Schiff (PAS) reagent. A search for infections at other sites such as the hands, feet (soles and webs), or groins, or the scalp in infants, should be instituted when there is a suspicion of onychomycosis. Discolored dyschromic nail changes caused by fungi are also considered in the section “Modification in color: nail dyschromia, or discoloration, or chromonychia” in Chapter 2.

**Distal and lateral subungual onychomycosis**

See Figs 12.3 and 12.4.

**Primary distal and lateral subungual onychomycosis**

In this pattern of infection (Table 12.1), the onychodermal band is disrupted by infection and the fungus reaches the underside of the nail via the hyponychium, the nail bed, or the lateral nail fold where the stratum corneum is invaded. The nail bed infection in distal and lateral subungual onychomycosis (DLSO) caused by *T. rubrum* is the result of the fungus spreading from the plantar [14] and palmar surface of the feet and hands [15]. The thickened horny layer raises the free edge of the nail plate with disruption of the normal nail plate–nail bed attachment [16]. The disease spreads proximally and the nail becomes opaque. Fungal invasion leads to orthokeratosis of the nail bed epithelium.
In advanced nail disease, a more severe inflammatory reaction affects the nail bed with penetration of mononuclear cells and polymorphonuclear leukocytes into the subungual keratin, sometimes mimicking Munro's microabscesses. Parakeratotic foci, often containing inspissated serum, may appear [17]. In time, tunnels or lacunae produced by dermatophytes and containing air and softened keratin, described [18] as a transverse net, appear as opaque streaks in the nail plate. Occasionally, this may be seen more clearly with the aid of a lens, after the nail plate has been treated with cedar oil to render it translucent. Where the network is sufficiently dense, with huge masses of compressed fungal elements (dermatophytoma) it appears as an opaque white or yellowish zone or streak (Fig. 12.5), a clinical feature often seen in dermatophyte or mold infections. Such lacunae often contain masses of fungi as well as keratin debris and their

Figure 12.2 (a) Distal and lateral subungual onychomycosis presenting as one-hand/two-feet tinea syndrome by *Trichophyton rubrum*. (b) Involvement of the palm of the same hand.

Figure 12.3 (a, b) Distal and lateral subungual onychomycosis due to *Trichophyton rubrum*.

Figure 12.4 Distal and lateral subungual onychomycosis restricted to the lateral edges (a). Histology of the same patient shows onycholysis (b). Courtesy of R. Rodriguez.
existence provides a difficult target for treatment as persistence of infection may occur at this site, possibly due to poor drug penetration. Often there is nail invasion in a longitudinal narrow band which follows the ridges of the nail bed. With progressive fungal infection, the nail becomes friable and eroded at the lateral and distal borders. In addition, a variety of microorganisms may coexist in the ecological niche created by an area of onycholysis and these are responsible for nail color changes, which vary from gray to chestnut brown [19]. Erythrasma of the nail has been reported [20].

The clinical appearances of nail dystrophies caused by different fungi are seldom diagnostic, but there may be some useful and potentially distinctive features apart from the differences in the overall pattern of nail involvement discussed previously. For example, hyperkeratosis accompanying onycholysis is a common feature of dermatophyte infections (Figs 12.6, 12.7), which are the most common
causes of DLSO, whereas in *Candida* onychomycosis gross hyperkeratosis is mainly seen in total nail plate involvement in patients with chronic mucocutaneous candidiasis; in other cases of true *Candida* onychomycosis, thickening of the nail plate may be minimal (Fig. 12.8).

There has been some debate about the role of *Candida* as a cause of DLSO. *Candida* species are said not to produce specific keratinases and therefore they cannot invade the healthy nail plate. However, some patients present with a genuine distal and lateral invasion of the nail plate with erosion, confirmed histologically, but without significant thickening. This is mainly seen in patients with endogenous or exogenous Cushing syndrome or those with Raynaud phenomenon [21]. It may also occur in some tropical countries. While it is possible that some invasion is secondary to preexisting onycholysis, this is seldom possible to establish. There is often a distinctive brown- or cinnamon-colored discoloration of nails, mainly toenails, affected by *Scopulariopsis brevicaulis*. It is caused by the presence of large numbers of pigmented conidia produced in situ [22]. Likewise, brown pigmentation appearing as an irregular streak in the nail plate, often at the lateral border of the great toenail, is also a feature of infections caused by *Trichophyton interdigitale*, and *T. rubrum* may sometimes present with longitudinal melanonychia [23, 24]. Both fungi produce melanin.

The nail dystrophies caused by *N. dimidiatum* (Fig. 12.9a) or *N. hyalinum* are similar to dermatophyte onychomycosis [25–27] (Fig. 12.9b). However, secondary paronychia
appears to be more common in fingernail infections, and extensive onycholysis may also be a prominent feature of these infections. This may lead to a transverse fracture of the nail plate near the proximal nail fold and subsequent shedding of the distal plate. Paronychia associated with DLSO is also seen in some *Fusarium* infections.

On occasions, dermatophytes may be isolated from nails, such as the great toenail, which show idiopathic or primary onycholysis (Table 12.2). For instance, 9% of normal, healthy-looking nails (3955 samples) were positive for fungus on direct microscopy, culture, or both [28]. This was confirmed [29] when *T. rubrum* was found in the nails of four patients, *T. interdigitale* in two, and *Epidermophyton floccosum* in one in 46 samples of normal nails from patients infected in other sites. A subsequent control study was carried out on 52 outpatients seeking medical advice for reasons other than great toenail dystrophy. Dermatophytes were isolated from clinically normal great toenails in two patients: *T. rubrum* in one case and *E. floccosum* in the other. Subsequent experience confirms these observations. The presence of potentially pathogenic fungi in “normal” nails may herald the first stage of nail plate infection.

On the fingers, primary onycholysis is more frequently associated with secondary invasion by *Candida* (Fig. 12.10) and/or *Pseudomonas*; it is most common in women in whom there is repeated contact with water, soap, and detergents. Contrary to the classic pattern of DLSO, which usually starts with distal hyperkeratosis, there is a reversal of the usual order of evolution of each lesion in secondary onychomycosis. For example, in the fingernails, onycholysis precedes any subsequent thickening of the distal subungual...

---

### Table 12.2 Subtypes of chronic mucocutaneous candidosis (CMC). *

<table>
<thead>
<tr>
<th>Type</th>
<th>Pattern of inheritance</th>
<th>Special clinical/immunological features</th>
</tr>
</thead>
<tbody>
<tr>
<td>CMC</td>
<td></td>
<td>Childhood onset</td>
</tr>
<tr>
<td>Without endocrinopathy</td>
<td>Recessive</td>
<td>Childhood onset. Patients have the polyendocrinopathy syndrome</td>
</tr>
<tr>
<td>With endocrinopathy</td>
<td>Recessive</td>
<td>Childhood onset</td>
</tr>
<tr>
<td>Without endocrinopathy</td>
<td>Dominant</td>
<td>Childhood onset</td>
</tr>
<tr>
<td>With endocrinopathy</td>
<td>Dominant</td>
<td>Childhood onset. Associated with hypothyroidism</td>
</tr>
<tr>
<td>Sporadic CMC</td>
<td>None known</td>
<td>Childhood onset</td>
</tr>
<tr>
<td>CMC with keratitis</td>
<td>None known</td>
<td>Childhood onset. Associated with keratitis</td>
</tr>
<tr>
<td>Late-onset CMC</td>
<td>None known</td>
<td>Onset in adult life. Associated with thymoma</td>
</tr>
</tbody>
</table>

*While originally severe CMC (e.g. *Candida* granuloma) was described in association with specific subtypes, it is now apparent that extensive infection, including hyperkeratotic candidosis and dermatophytosis, is not specific to any one variety.

†McKusick numbers.

‡The main endocrine diseases seen with this variety are hypoparathyroidism and hypoadrenalism and have associated mutations in the autoimmune regulator (AIRE) gene.

#CMC with hypothyroidism is associated with mutations in the STAT1 gene.

§Other late-onset types have been recorded, e.g. with systemic lupus erythematosus, but as they are usually associated with systemic corticosteroid therapy, they have been excluded as secondary candidosis. Reproduced from Coleman and Hay [46] with permission from Wiley-Blackwell.
area, hence the name of DLSO associated with onycholy-sis. Repeated episodes of friction secondary to rubbing of the nails against shoes or the repeated episodic trauma incurred during running or jogging may also create an area of traumatic onycholysis where microorganisms are also potentially but not invariably pathogenic.

A variety of fungi, not normally considered pathogenic, may be isolated from dystrophic nails, particularly in the elderly [30]. The usual clinical pattern of nail involvement most closely resembles DLSO. Hyperkeratosis and brown or green discoloration are common and the toenails are most commonly affected. The organisms isolated may include *Aspergillus* species such as *A. terreus* or *A. versicolor*, *Acremonium* spp, *Penicillium* spp, and *Pyrenochaeta unguium hominis* [31]. As these organisms do not appear to be able to break down keratin, it is assumed that they are colonists of dystrophic or abnormal nails. It is, however, difficult to be certain that they are not contributing to the nail dystrophy, hence repeated isolation of the same organism is an indication for treatment. There is some evidence that some of these species (e.g. *Acremonium* spp) produce perforating organs, specialized hyphal structures usually associated with hair invasion, analogous to those seen in dermatophytosis. Other non-dermatophyte fungi invading nails such as *S. brevicaulis* can be demonstrated by electron microscopy inside keratinized cells [9]. *Neoscytalidium* species, pathogenic in humans, produce keratinases.

Other yeasts may also be isolated from the same site. These include *Candida* species such as *C. guilliermondii*. As with the molds discussed above, it is assumed that they are secondary invaders. The distinction between nail pathogens and opportunistic organisms which inhabit nails under abnormal conditions is a tenuous one. As has been seen above, even the dermatophytes can be secondary invaders [32]. Likewise, *S. brevicaulis* is often merely a colonist.

The clinical significance of nail invasion or colonization by fungi which are not normally pathogenic needs to be carefully considered in the light of laboratory findings such as the results of nail biopsy. It is likely that organisms which colonize nails may play a more destructive role if the host’s immune defenses or the nail matrix are altered by disease or another infection. Equally, their removal may simply be “academic” if the nail dystrophy remains after antifungal therapy.

**Superficial onychomycosis**

**Superficial white onychomycosis**

Superficial white onychomycosis (SWO) is fairly rare and is normally confined to the toenails (Figs 12.11–12.13; see also Table 12.1). Here the upper surface of the nail plate is the initial site of invasion. The causative organisms produce a clinical picture of small superficial white patches with distinct edges [33]. These later coalesce and may gradually cover the whole nail, hence the term leukonychia trichophytica (mycotica). The chalky white surface becomes roughened and the texture softer...
than normal. The appearance has been likened to “paper-bark,” the affected nail plate crumbles easily and old lesions acquire a yellowish color. In other cases, the superficial infection is arranged in linear bands (striate leukonychia); in some such cases, the infection appears to emerge from under the nail fold. Patchy superficial onychomycosis may also emerge from under the nail fold. In such cases, there is often associated proximal subungual onychomycosis (see “Proximal subungual onychomycosis”) [34]. This type of nail invasion is caused by \textit{T. interdigitale} in many cases. Using epiillumination microscopy, the individual white flakes representing colonies of \textit{T. interdigitale} can be observed clearly. Patches of SWO are not uncommonly seen in areas where the nail is occluded, for instance by an overlying adjacent toe.

Infections caused by non-dermatophytes such as \textit{Aspergillus terreus, Fusarium oxysporum, or Acremonium spp} are more often seen in patients in warmer climates. \textit{Candida albicans} has occasionally been isolated in infants [35]. In HIV-infected or immunocompromised patients, SWO is not rare in finger or toenails and is often due to \textit{T. rubrum} or \textit{Fusarium}. However, here the pattern of infection is usually different, as there is often proximal subungual infection as well (see “Proximal subungual onychomycosis”). Likewise, superficial nail plate invasion in the immunocompromised can be accompanied by deep penetration by fungal hyphae into the nail plate with extensive infiltration of the nail [36].

**Superficial black onychomycosis**

A similar pattern of nail plate invasion and dystrophy may be caused by dematiaceous or black fungi (Fig. 12.14). These are rare but \textit{N. dimidiatum} [37, 38] and \textit{T. rubrum} [37] have been described as possible causes.

**Endonyx onychomycosis**

In endonyx onychomycosis (Fig. 12.15), infections of the fingernails due to the dermatophytes which cause endothrix scalp infections may present with less nail
plate thickening, but the plate is pitted and the distal margin covered with lamellar splits [39]. These changes have been studied in detail [40] and shown to consist of areas of superficial nail plate invasion but with deep penetration, and fungal hyphae are seen within the nail plate. The nail surface has lamellar-like splits and the end of the nail plate is often friable and split. However, hyperkeratosis is minimal and dense opacification is unusual. These changes are typical of invasion caused by *Trichophyton soudanense* but similar changes have been seen with *T. violaceum* and *T. tonsurans*.

**Proximal subungual onychomycosis**

See Table 12.1.

**Proximal white subungual onychomycosis**

Proximal white subungual onychomycosis (PWSO) is rare and affects both fingernails and toenails (Figs 12.16–12.18). The causative organisms were thought to penetrate via the proximal nail fold, the stratum corneum of which was the primary site of the fungal invasion. However, there
is no histological proof that this is the route of invasion and other routes of entry have been proposed. Among these, the possibility that invasion of the proximal nail plate follows spread through either local blood vessels or lymphatics has been raised [41]. The evidence is based on the observation of bloodstream dissemination of nail fungi, e.g. in deep dermatophytosis or fusariosis, as well as deep lymphatic spread in some patients. When reaching the matrix, the fungus would then invade the undersurface of the nail plate. A white spot appears from beneath the proximal nail fold and, although it is confined initially to the lunula area, when the white spot moves distally it remains in the same layer of the nail plate. The fungus has to invade more distal parts of the matrix to become entrapped in the deeper layers of the nail plate. This is sometimes accompanied by slight discomfort. This pattern may also be seen where there is a recurrence of nail infection in an incompletely treated nail. Once again, a striate leukonychia pattern has also been seen and in some cases this coexists with superficial onychomycosis of the striate pattern, less often with the more common patchy superficial onychomycosis [34]. This type of nail invasion is usually caused by *T. rubrum* but *T. megnini, T. schoenleinii*, or *E. floccosum* may be seen. *Fusarium* species have also been recorded as causes.

A rapidly developing form of PWSO has been recorded in immunosuppressed patients, including those with AIDS. Here, the infection may spread rapidly under the nail from the proximal margin of all the finger and toenails [42]. Histopathology shows that the entire nail plate is infiltrated with fungi, which are lying in a longitudinal

![Figure 12.17](a) Proximal white subungual onychomycosis (PWSO) with dystrophic keratin of the superficial nail plate. (b) PWSO as longitudinal leukonychia appearing from beneath the cuticle. Courtesy of B. Schubert.

![Figure 12.18](a) Proximal white subungual onychomycosis (PWSO) in AIDS. (b) PWSO involving several digits at the same level. (c) PWSO single transverse leukonychia due to *Trichophyton rubrum*. (d) PWSO double transverse band separated by normal pink nail due to *T. rubrum*. Courtesy of B. Richert. (e) PWSO. Several bands separated by normal nail, due to *T. rubrum*.
parallel arrangement. However, the picture is complicated in that other surfaces such as the superior aspect of the plate and the distal or lateral margins may also be involved. Possibly because of the rapid spread, these patients do not show much nail thickening [43].

**Proximal subungual onychomycosis secondary to paronychia**

Nail plate invasion may occur secondary to paronychia from which fungi such as *Candida* as well as *Fusarium* and *Neoscytalidium* have been isolated (Fig. 12.19). This is usually a lateral form of proximal subungual onychomycosis in the case of *Candida*, although with *Neoscytalidium* and possibly *Fusarium* the infection appears to spread from the distal nail plate and the onychomycosis in these cases is more correctly described as DLSO. Fungal elements can be seen by microscopy in the nail plate, thus confirming the diagnosis.

**Total dystrophic onychomycosis**

Total dystrophic onychomycosis or totally dystrophic onychomycosis (TDO) represents the most advanced form of all the four previous types described above, especially DLSO (see Table 12.1) (Figs 12.20–12.26). The nail crumbles and disappears, leaving a thickened and abnormal nail.
bed that usually retains fragments of nail plate. All 20 nails may be involved in chronic generalized dermatophytosis [44, 45]. In the new form of total nail dystrophy observed in patients with AIDS, infection appears to have spread from under the proximal nail fold (proximal subungual onychomycosis), but this has not been established in all cases. The dorsum of the nail plate may also be involved. The term “acute TDO” might be appropriate for this type of infection. In contrast to secondary TDO, primary TDO is observed only in patients with chronic mucocutaneous candidiasis (CMC) or other immunodeficiency states (Table 12.2) [46]. Candida invasion rapidly involves all the tissues of the nail apparatus. The thickening of the soft tissues results in a swollen distal phalanx more bulbous than clubbed. The nail plate is thickened, opaque, and yellow-brown in color. Hyperkeratotic areas secondary to Candida invasion may develop in skin adjacent to the nail. Oral candidiasis is generally present in these patients. This syndrome, which usually occurs in childhood or infancy, recurs despite treatment. Dual or sole infection...
Fungal (Onychomycosis) and Other Infections Involving the Nail Apparatus

with dermatophytes may occur in patients with CMC. There is no evidence that the different clinical forms of CMC are associated with different patterns of nail disease (Table 12.2).

**Mixed pattern onychomycosis**

Although the different patterns of onychomycosis have been described as distinct entities, they may also coexist so that a patient may, for instance, show DLSO and subungual onychomycosis or, as described above, proximal subungual onychomycosis and subungual onychomycosis on the same nail plate.

**Secondary onychomycosis**

Fungal infection of the nail plate may develop secondary to some other dermatological condition. The best known example is psoriasis [47], but the same may occur secondary to keratodermas or onychogryphosis. The importance of recognizing this is that the nail appearances associated with the underlying disease generally obscure those due to the fungus.

**Paronychia**

Paronychia is observed most commonly in adult women and affects particularly the index and middle fingers and thumb of the dominant hand. Frequent manual work with carbohydrate-containing foods and moisture, maceration, occlusion, hyperhidrosis, and acrocyanosis favor the disease. In children, finger sucking is a cause of paronychia [48]. Diabetes mellitus and other hormonal disturbances and drugs such as corticosteroids, cytotoxics, and antibiotics may exacerbate *Candida* paronychia.

The first step in the development of chronic paronychia is mechanical infection or chemical trauma that produces cuticle damage. At that time, the epidermal barrier of the ventral aspect of the proximal nail fold is destroyed and the area is suddenly exposed to a variety of environmental hazards. Irritants and allergens may then produce an
inflammatory reaction of the nail fold and nail matrix, which interferes with the normal nail growth. Usually the nail fold inflammation affects the lateral portion of the matrix, leading to nail plate deformity on the same side, appearing as irregular transverse ridging or a dark narrow strip down one or both lateral borders of the nail.

The thickened free end of the erythematous proximal nail fold becomes rounded and retracted and loses the ability to form a cuticle. The disease tends to run a protracted course interrupted by subacute exacerbations due to secondary Candida and bacterial infection with the formation of a small abscess in the space formed between the proximal nail fold and the nail plate. Candida spp and bacteria are frequently isolated from beneath the proximal nail fold in patients with chronic paronychia [49].

Depending on the major etiological factors involved, it has been proposed that chronic paronychia can be classified into the following types [50].

- Contact allergy (topical drug ingredients, rubber, etc.) [51].
- Food hypersensitivity (a variety of immediate contact dermatitis due to foods).
- Candida hypersensitivity (a similar reaction to that suggested in some patients with recurrent vaginitis).
- Irritative reaction (irritative chronic paronychia may subsequently acquire a secondary hypersensitivity and develop chronic food hypersensitivity paronychia and/or Candida hypersensitivity paronychia).
- Candida paronychia. True Candida paronychia is uncommon in temperate climates except in patients with CMC and HIV infection. In this condition, proximal nail fold inflammation is usually associated with proximal onycholysis or onychomycosis due to Candida, which can be isolated from both the proximal nail fold and clipping of the affected nail plate. In contrast to Candida infection, non-dermatophyte molds such as Fusarium (Fig. 12.19e) may produce subacute paronychia accompanied by proximal white onychomycosis, especially in immunocompromised individuals [52]. In Fusarium infection, subsequent disseminated spread of the organism to affect other sites in severely neutropenic patients may be preceded by a type of cellulitis proceeding from the nail fold [53]. Fusarium may also occasionally cause paronychia without nail plate invasion. Scopulariopsis brevicaulis may be responsible for identical features with a white or yellow discoloration of the nail plate [54]. Proximal subungual onychomycosis may also be associated with marked periungual inflammation and black discoloration of the lunula region due to Aspergillus niger [55].
- On rare occasions, other infections may involve the nail fold, causing a form of paronychia. Among the fungi, the agents of sporotrichosis and, less commonly, chromoblastomycosis, coccidioidomycosis, paracoccidioidomycosis, blastomycosis, and mycosis may involve this area.
- Bacterial paronychia. Bacteria may play a role in the pathogenesis of paronychia associated with Candida (see bullet point above). In addition, Staphylococcus aureus may cause an acute paronychia in an otherwise healthy patient. This generally arises as a result of an acute nail fold infection or whitlow and the nail fold may become swollen with subsequent discharge of pus via this area. Alternatively, chronic paronychia caused by S. aureus is not infrequently seen in patients with skin disease, such as psoriasis or eczema, affecting the nail fold. Generally these are difficult to distinguish clinically from Candida infections. Pseudomonas infection of the proximal nail fold may produce transverse green stripes on the nail corresponding to exacerbations of the paronychia [56] (Fig. 12.19f).
- Paronychia caused by foreign bodies [57, 58].

In practice, several of these factors may contribute in individual patients and the presence of Candida in nail fold biopsies is more common than might be expected (Hay, Doss, Baran, and Salisbury, personal observation). Likewise, whatever the original etiology, bacterial growth is also common.

**Diagnostic investigations**

**Dermoscopy**

The different types of onychomycosis have particular dermoscopy features, which can be observed even with a manual dermoscope [1–4]. Although the diagnosis of onychomycosis requires positive mycology or histopathology examination, nail dermoscopy is easy to perform, non-invasive, and gives important help especially in differential diagnosis with other non-mycotic nail diseases. Dermoscopy can also be utilized to locate the best proximal site for mycological sampling through abrasion [5].

**Dermoscopy in distal and lateral subungual onychomycosis**

Dermoscopy is performed with transparent ultrasound gel for immersion, and observation should focus on the shape of the proximal margin of the detachment, and on the color of the nail plate. Dermoscopy features specific of DLSO include:

1) Jagged edge of the proximal margin of the onycholysis, which shows sharp structures directed towards the proximal fold, called “spikes” (Fig. 12.27). These spikes derive from subungal hyperkeratosis along the horny layer of the proximal nail bed and indicate proximal progression of infecting dermatophytes. Their observation allows differential diagnosis with traumatic onycholysis, where the margin of the onycholysis is linear, and nail bed psoriasis, where it is slightly dented.
2) White to yellow, orange, and brown longitudinal striae in the onycholytic nail plate, often not detectable with the naked eye (Fig. 12.28).

3) Yellow-orange-brown discoloration of the affected nail plate, arranged in parallel bands of fading color, resembling the aurora borealis (aurora borealis pattern) [1].

Other dermoscopy features typical of but not exclusive to DLSO include the “ruin-like appearance” of subungual keratosis attached to the ventral nail plate, consisting of scales and hyphae, most evident at the distal margin of the nail plate [2], and distal irregular termination, due to extreme nail plate fragility and fragmentation following fungal invasion, detectable both in DLSO and in total onychomycosis [3]. Dermoscopy of a “dermatophytoma” shows an irregular, round, discolored area under the nail plate, with yellow-orange homogeneous matt color, connected with the distal margin by a longitudinal yellow-white band. In fungal melanonychia, dermoscopy allows differentiation from other causes of black pigmentation of the nail, including subungual hematoma and longitudinal melanonychia, as it shows that the nail pigmentation results from irregular accumulation of black pigment and scales under the nail plate (multicolored pigmentation [6] (Fig. 12.29) often arranged in longitudinal bands [7].
Laboratory investigation

Direct microscopy

Small pieces taken from clinically infected areas of nail and particularly of subungual hyperkeratosis are treated with 10–30% potassium hydroxide (KOH). To hasten clearing of the nail, the slide may be warmed over a Bunsen flame. The softened nail is flattened with gentle pressure applied to a coverslip. A formulation of KOH and dimethylsulfoxide [59] has been recommended. Sixty milliliters of a 20% KOH solution is mixed with 40 mL of pure dimethylsulfoxide. This technique is useful for the preservation of specimens, but globular artifacts may sometimes be seen and these must be distinguished from yeasts.

There are other techniques in which stains are used to highlight the presence of fungi. These are often very useful in difficult cases. One such technique, useful in non-dermatophyte infections, is an equivolume mixture of Parker permanent blue ink and 10–20% KOH [60]. Spores of non-dermatophyte fungi and some mycelial elements are highlighted using this technique. The stain, chlorazol black (which is not available in all countries), is also useful for highlighting hyphae in direct material taken from nails. Calcofluor white, a fluorescent whitening agent mixed with an equal volume of KOH, may also be used to highlight, non-specifically, the fungal elements in nail in direct microscopy [60]. Fluorescent whiteners specifically bind to structural proteins of plants, for example chitin and lignin, but not to keratin and other animal proteins; the physicochemical process is called substrate binding. Rapid staining of the nail plate using a modification of the PAS stain is also very effective at highlighting fungi in nail material (see “Histopathology for demonstrating fungi in the nail”).

The nail is examined for fungal hyphae or arthrospores. In Candida infections, yeast forms are also present. In certain non-dermatophyte infections conidia may be formed in situ. This is characteristic of Scopulariopsis infections, although it may also occur in onychomycosis caused by Aspergillus species. The hyphae of N. dimidiatum and N. hyalinum are very similar in appearance to those of dermatophytes, although they may appear thinner, irregular, and more sinuous. This is seen best with phase contrast illumination (Fig. 12.30).

At present, a more specific system for immunological detection of fungi in nails, such as the use of fluorescein-conjugated antidermatophyte antibodies, has not been widely applied in medicine, although this technique [61], along with another using fluorescent lectin stains which bind differentially to different nail fungi, has been assessed (see “Histopathology for demonstrating fungi in the nail”) [62].

Culture [63–67]

Scrapings from subungual keratosis and nails should be planted into Sabouraud agar and incubated at 26°C (Figs 12.31, 12.32). The different organisms can be recognized using morphological and/or biochemical criteria. The presence of chloramphenicol or streptomycin and penicillin in the medium prevents the growth of contaminant bacteria. However, wherever possible, nails should be plated on medium both with and without cycloheximide (actidione), as it inhibits some non-dermatophytes that may cause onychomycosis.

It is sometimes difficult to isolate fungi, even from nails which are positive on direct microscopy. The problem is compounded if the patient has already received...
topical or systemic treatment and if the hyphae in the most accessible part of the nail plate are not viable [68]. In order to improve the isolation rate, various methods have been devised. These include the use of a grinder [69, 70] or a dental drill fitted with a suction nozzle, which collects the nail dust for microscopy and culture [71]. This latter instrument has raised the success rate of culture from microscopically positive nails from the usual rate of 50–75% to about 88%, but is not a practical procedure for the routine laboratory.

Scopulariopsis brevicaulis forms filaments as well as spores of characteristic size and morphology in nail. The demonstration of *S. brevicaulis* on direct microscopy and the presence of more than 10 colonies in culture is thought to be diagnostic of infections caused by this organism [72]. If there are fewer than three colonies, and *S. brevicaulis* is not seen on direct microscopy, the organism is probably present as a commensal. *Scopulariopsis brevicaulis* is often found in toenails infected by dermatophytes, particularly *T. rubrum* or *T. interdigitale* [73]. The dermatophyte responsible for the primary infection may eventually be isolated after repeated scrapings have been taken. *Aspergillus* spp may also form conidia in nails in vivo.

It has been suggested [74] that the following criteria are helpful in determining whether a fungus is merely a commensal or whether it is truly responsible for nail dystrophy.

- If a dermatophyte is isolated, it is considered to be the likely pathogen.
- If molds or yeasts are isolated, they are thought to be significant only if mycelia, arthrospores, or yeast cells are found on direct microscopic examination of the nail specimen.
- Final confirmation of mold infection requires isolation of the mold on at least five out of 20 inocula, in addition to the absence of dermatophytes on either actidione-containing or actidione-free media.

Most clinicians would find these criteria too stringent with repeated cultures being considered acceptable, although they provide a useful guideline. They are also questionable since, in onycholysis of certain nails such as the great toenail, cultured dermatophytes may be present as commensals [32]. The clinical appearances of the nails, tortuous or “atypical” hyphal elements in nail clippings, and repeated isolations of a non-dermatophyte are all helpful clues to the possible involvement of an unusual organism. Likewise, the presence of *Candida* species in material taken from under nails with onycholysis does not appear to be diagnostic of invasion of the nail plate, certainly if only yeast forms are seen on direct microscopy [21]; the presence of *Candida* mycelium in nail material and the growth of *C. albicans* is more likely to imply a pathogenic role for these organisms in nail dystrophy. Similarly, *Malassezia* species have been described in patients with onycholysis. It has been suggested that they are pathogens in view of the treatment response of some cases to antifungal therapy [75]. However, these observations should be interpreted with caution, as patients with idiopathic onycholysis show spontaneous remission; these lipophilic yeasts may simply be commensals of onycholytic nails. A study of the use of terbinafine showed that the clinical response of nails to treatment with terbinafine was dependent on the response of dermatophytes and that mold or yeast fungi isolated from the nails came and went but their presence had no effect on the response to treatment.

Histological examination of the nail plate, with the underlying tissue, will not only demonstrate the fungal elements but also reveal the depth of their penetration into the nail plate. This may provide further evidence of the pathogenic role of fungi isolated in culture, particularly if they can be identified in situ on morphological grounds, or by immunofluorescent labeling using specific antisera (see “Direct microscopy”).

**Histopathology for demonstrating fungi in the nail** [76–88]

Histopathology can demonstrate whether a fungus is invasive or merely colonizing subungual debris (Figs 12.33–12.45). Depending on the site of the pathology, nail clippings should be taken from the edge or the lateral part of the nail plate together with a shallow
portion of subungual tissue (see Chapter 22). They are then embedded directly into paraffin without using a fixative. The specimens are stained with hematoxylin and eosin, PAS, and toluidine blue; calcofluor and Grocott’s stain can also be used. The fungi can be seen in the subungual keratin and undersurface of the nail plate.

Histopathological examination of nail clippings with subungual keratosis very often shows fungal elements even when cultures are repeatedly negative. Nail clippings may be embedded in paraffin without prior fixation. However, some softening techniques may be applied beforehand to facilitate sectioning. The use of a chitin-softening solution containing mercuric chloride, chromic acid, acetic acid, and 95% alcohol has been advocated as a means of enhancing the quality of the histological sections [83]. PAS stain is usually sufficient to demonstrate fungi; however, small serum inclusions may be mistaken for fungi by the inexperienced as they are also PAS positive [81, 82, 89]. However, rapid PAS staining techniques are available and can be applied to the nail. The methenamine silver stain (Grocott) and calcofluor are more selective [81, 82]. The fungi are usually located in the subungual keratosis, but may have invaded the deepest parts of the nail plate. Histopathology shows whether the fungi are invasive or only contaminants, for example spores in clefts of the subungual keratin. Fungi cannot be further identified, since both dermatophytes and molds may produce hyphae and large, thick-walled arthrospores. However, some fungi do produce distinctive morphological features in nail which aid identification, for example yeasts plus hyphae and
Fungal (Onychomycosis) and Other Infections Involving the Nail Apparatus

pseudohyphae with *C. albicans* or rough surfaced conidiospores with *S. brevicaulis*.

Nail clippings often show abundant Munro-like abscesses in onychomycosis; since fungi may be sparse, one cannot make the diagnosis of nail psoriasis from the presence of intracorneal abscesses in the absence of fungi alone. If the hyponychium is not affected, any non-dermatophyte fungi cultured from the nails should be regarded as contaminants. However, if fungi can be demonstrated histologically in the hyponychium of a nail from which fungi have not been isolated, the culture result is clearly false negative. This view is supported by therapeutic investigations [63, 90] that have shown that treatment with griseofulvin affects the form and position of the fungus in relation to keratin in patients with microscopically visible fungi, by allowing nail growth to carry hyphal tips to the free edge of the nail. This may account for the positive results using the staining techniques described above in cases where repeated culture has been negative. For the early diagnosis of PWSO, a 3-mm punch biopsy taken from the proximal white area and restricted to the
nail plate is indispensable. The hyphae are located in the deeper portion of the nail plate and the keratinized cells in the adherent superficial layers of the nail plate. The flattened filaments lie parallel to the nail surface and “worm” their way into the intercellular spaces.

Another technique which can be used to highlight fungi in nail biopsy material is a fluorescein-conjugated lectin stain (for instance, concanavalin A) on nail biopsies softened with 10% KOH. Fungal elements are strongly stained with the lectin conjugate [62].
Histopathology of nail biopsies has given considerable information concerning the pathogenesis of onychomycoses. It also allows one to subdivide the various clinical types of onychomycoses and provides convincing evidence of the different routes of infection and ports of entry.

DLSO develops from an infection of the hyponychium and almost invariably shows fungi in the hyperkeratosis of the distal nail bed. The fungi progress towards the matrix and induce mild inflammation. This causes an “epidermization” of the nail bed with the formation of a pronounced granular layer and a thick, mainly orthokeratotic, horny layer. The latter is protected by the overlying nail plate, preventing its desquamation and keeping it moist and soft. This gives an ideal microenvironment for the fungi, which are often present in very large amounts. The nail plate is invaded from its undersurface with the hyphae showing a parallel, often longitudinal arrangement. High-power magnification frequently shows tunnels in the nail substance, the diameter of which are considerably greater than those of the fungi; they are seen macroscopically as a transverse net [18]. The subungal keratosis may be secondarily colonized by opportunistic bacteria and fungi, which may produce discoloration, friability, and loss of luster of the nail.

Longstanding fungal infections may cause severe inflammatory changes with spongiosis, exocytosis of lymphocytes and polymorphonuclear leukocytes, and papillomatosis of the nail bed. The subungal keratosis then contains globules of serum and abundant microabscesses, but the keratosis is still mainly orthokeratotic. When the nail plate is destroyed, the parallel longitudinal arrangement of the fungi gets lost and the fungi crisscross the subungal keratin and nail plate remnants in an irregular arrangement.

Bacterial colonization may be seen, mostly as a line of small basophilic coccoid organisms. In onychomycosis nigricans, the nail plate and even a portion of the subungal keratosis are diffusely yellowish-brown to dark brown, and there is no specific pigmented change [17]. Occasionally, a whitish-yellow longitudinal band is seen extending from the hyponychium towards the matrix; this is often left after an otherwise successful treatment of onychomycosis of the toenail and does not respond to further systemic antifungals.

Histopathology reveals a PAS-positive globus consisting of a huge amount of densely packed fungal elements, mainly arthrospores but also hyphae.

Proximal subungal onychomycosis due to Candida develops from infection of the proximal nail fold. Histopathology shows fungi in the cuticle, a hyperkeratotic eponychium with fungal invasion, and usually a mild inflammatory infiltrate beneath the epidermis of the eponychium. The hyphae with yeasts may invade the nail plate surface but are often confined to one area. In other forms of proximal subungal onychomycosis, notably that caused by dermatophytes, there is no evidence that penetration of the nail plate occurs following penetration from the nail fold. In established infection, both hyphae and thick arthroconidia may be seen in different layers of the nail plate, often causing microscopic slits which may abruptly extend to cause onycholysis presenting as apparent leukonychia. In advanced proximal subungal onychomycosis, changes may be as severe as in DLSO [81, 89].

In SWO, there are chains of round arthroconidia in the nail plate extending in between superficial splits of the nail. There is no inflammatory infiltrate in the nail bed beneath [81, 82].

Primary TDO is a characteristic feature of CMC [89] and both DLSO and proximal subungal onychomycosis may lead to secondary TDO.

TDO in CMC is characterized by a complete loss of the ordered nail structure. The proximal nail fold may have been reduced to a small rim of tissue, the cuticle is lost, matrix and nail bed are papillomatous and covered with a thick irregular keratosis, and there is a heavy inflammatory infiltrate invading matrix and nail bed epithelium. Electron microscopic investigation shows composite keratohyalin granules in the matrix. Fungal elements are seen in variable amounts. When they form hyphae, they are irregularly arranged, because there is no orderly nail plate growth left [89].

Molecular diagnosis

The use of molecular methods to detect fungal DNA or RNA in nail fragments is gaining popularity. However, at present there are only a few commercially available systems for diagnosis and routine use of these techniques is only applied in a few laboratories. Generally these use either one or more probes that are specific to common organisms such as T. rubrum or panfungal probes that detect a wider range of organisms. At present, there is
some difficulty in determining specificity versus carriage/true infection. Some authors advise using an algorithm which utilizes direct microscopy as the first measure followed, where necessary, by molecular testing using a polymerase chain reaction technique. This method is likely to become more common in the future as microbiology laboratories adopt molecular diagnostic tools [91].

**Differential diagnosis**

Subungual hyperkeratosis, onycholysis, leukonychia, splinter hemorrhages, as well as dystrophy involving the whole nail plate may be seen both in dermatophytosis and in psoriasis, and it may be impossible to diagnose isolated psoriasis of the nails on clinical grounds unless there is extensive pitting and/or the oil drop sign. Nail clippings or, in total nail dystrophy, a shave biopsy from the hyperkeratotic zone of the affected nail bed may be helpful in differentiating between psoriasis and dermatophytosis [92, 93]. Parakeratosis and neutrophils within this zone can be seen in both conditions. Koutselinis et al. [94] suggested that, in clinical practice, surface and subungal scrapings are satisfactory for the cytological diagnosis of psoriasis; the skin surface biopsy technique [95] may be used similarly.

In psoriasis, neither hyphae nor spores are found in the cornified cells of the nail bed nor in the lowest portion of the nail plate. However, dual pathologies do occur and psoriatic nails, particularly toenails, may be associated with commensal fungi as secondary colonization or invasion caused by *Candida* or dermatophytes. Recent studies suggest that the incidence of dermatophytosis of the nails is higher than previously thought in patients with psoriasis [47]. Dermatophyte infections may involve the nails in Darier disease, lichen planus, and ichthyotic states such as the KID (keratosis, ichthyosis, and deafness) syndrome. The yellow nail syndrome may also be mistaken for a fungal infection; however, the hardness of the nail plate, its increased longitudinal curvature, and the light green-yellow discoloration are all typical. The irregularly buckled nail of eczema and the ridged or dystrophic nail of lichen planus must be distinguished from onychomycosis.

**TREATMENT**

**Casey Wang, Nikki Sullivan, and Boni Elewski**

Therapy for onychomycosis continues to remain a challenge for patients and clinicians despite improvements in the last decade with the development of new antifungal drugs and devices. In this section, current and experimental therapies for onychomycosis will be discussed, with attention to success rates and major side-effects as well as their advantages and disadvantages. Treatment options can be divided into three broad groups: topical therapies, systemic therapies, and non-drug device therapies. Topical therapies are often preferred by patients because of the favorable side-effect profile and the lack of laboratory monitoring. Additionally, innovative therapies are in development, including the use of devices such as lasers and photodynamic therapy with blue and red light sources.

It is important to note that discussions of treatment efficacy will refer to published cure rates from recent and older clinical trials (Table 12.3). Comparisons between studies are complicated by the fact that studies differed in the definitions of cure rates as well as other criteria such as subject age range and disease severity. In most recent studies, mycological cure is defined as negative KOH preparation and fungal culture. Clinical cure is defined as normal appearance of the nail (0% nail involvement). Complete cure is the combination of clinical and mycological cure. A study may define “clinical success” as less than 5–10% target nail involvement in addition to negative mycology.

### Table 12.3 Comparative efficacies of antifungal agents for onychomycosis.

<table>
<thead>
<tr>
<th>Agent</th>
<th>Mycological cure rate (%)</th>
<th>Complete cure rate (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Topical agents</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Amorolfin 5%</td>
<td>71.2–75.3</td>
<td>45.6–51.8*</td>
</tr>
<tr>
<td>Ciclopirox 8%</td>
<td>29–36</td>
<td>5.5–8.5</td>
</tr>
<tr>
<td>Tavaborole 5%</td>
<td>31.1–35.9</td>
<td>6.5–9.1</td>
</tr>
<tr>
<td>Efinaconazole 10%</td>
<td>53.4–55.2</td>
<td>15.2–17.8</td>
</tr>
<tr>
<td><strong>Systemic agents</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Terbinafine</td>
<td>70</td>
<td>38</td>
</tr>
<tr>
<td>Itraconazole</td>
<td>54</td>
<td>14</td>
</tr>
<tr>
<td>Meltrex/itraconazole</td>
<td>44</td>
<td>22</td>
</tr>
<tr>
<td>Fluconazole</td>
<td>47–62</td>
<td>37–48</td>
</tr>
<tr>
<td>Posaconazole</td>
<td>70</td>
<td>54</td>
</tr>
<tr>
<td>ALA-PDT</td>
<td>43*</td>
<td></td>
</tr>
</tbody>
</table>

*Complete cure was defined in most studies as negative mycology in addition to no nail involvement. However, amorolfin studies considered cases with less than 10% target nail involvement and negative mycological culture to be “completely cured,” perhaps accounting for the higher complete cure rates reported in amorolfin studies.

†Negative fungal culture and potassium hydroxide at end of study.

‡Per package label.

§Cure rate for ALA-PDT study includes patients with 0% nail involvement and those with <10% involvement in addition to negative mycology.

### Candidates for topical therapy

**Topical therapies**

Historically, onychomycosis treatment has required the use of systemic antifungal drugs owing to the challenge of drug delivery to the nail bed. In recent decades, topical therapy for onychomycosis has been made possible by
the development of several novel antifungal drugs, which have been formulated in a solution vehicle to demonstrate high nail permeation and improved clinical efficacy. Topical therapy has the perception of safety, and does not require periodic laboratory monitoring. Comorbidities such as heart or liver disease may preclude the use of oral drugs, and drug–drug interactions may also be a limiting factor.

Topical antifungals also have drawbacks, which can be amplified in elderly patients in whom the disease is most prevalent. Treatment is generally until the nail has grown out and may extend to more than 1 year. In the elderly this may take even longer because of slower nail growth. Adherence to a daily topical treatment may be challenging in patients with limited mobility or who are unable to reach their feet because of obesity or joint disease. Finally, topical formulations can be very expensive and are not always covered by insurance providers.

When determining if a patient should be treated with a topical agent for onychomycosis, many factors should be considered. First, the diagnosis must be established with a positive KOH examination, a positive fungal culture for a dermatophyte, or a PAS stain showing septate hyphae. Poor prognosis may be associated with nail matrix or lunula involvement, infection close to the proximal nail fold, presence of a dermatophytoma, thick nail plates (>2–3 mm), or significant involvement of a nail. These factors may preclude treatment with topical agents.

The azoles
The azoles are a large class of antifungals that can be subdivided into imidazoles (tioconazole, bifonazole, luliconazole) and triazoles (fluconazole, itraconazole, efinaconazole) based on their molecular structure [96].

Efinaconazole (Fig. 12.46a–c)
Efinaconazole is a triazole antifungal developed specifically for the treatment of onychomycosis, and is applied once daily directly to the nail plate and surrounding skin. It has demonstrated low affinity for keratin, which enhances nail permeation, as well as high subungual spreading, likely due to the cyclomethicone content [97, 98]. A study of 11 patients with moderate to severe onychomycosis demonstrated that efinaconazole concentrates on the nail bed after diffusion through the nail plate [98]. Efinaconazole is available in the USA and Canada as a 10% solution.

In two large 52-week parallel phase III trials including 1655 subjects aged 18–70, efinaconazole 10% solution applied daily for 48 weeks demonstrated complete cure rates of 17.8% and 15.2%, mycological cure rates of 55.2% and 53.4%, and clinical cure rates of 21% and 18%. Additionally, 35.7% and 31.0% achieved treatment success defined as ≤10% target nail involvement [99]. Phase III trial results also showed that clinical cure rates as high as 29% can be achieved if coexisting tinea pedis is also treated [100]. A post hoc analysis of phase III study results concluded that efinaconazole is similarly effective in patients with diabetes [101]. This is significant given that patients with diabetes are especially vulnerable to poor outcomes secondary to onychomycosis, such as infection and non-healing wounds.

Luliconazole
Luliconazole is a novel broad spectrum imidazole that has demonstrated potential for the treatment of onychomycosis but is currently only available as a 1% cream for the treatment of superficial mycoses. In the USA, luliconazole solution for the treatment of onychomycosis completed phase I/II studies in 2014 with favorable results. The trial enrolled more than 334 subjects and evaluated several dosing regimens [102]. In another open-label study of 24 patients, luliconazole 10% solution demonstrated a favorable safety and tolerability profile [103].

A Japanese in vitro study compared luliconazole 5% solution and efinaconazole 10% solution and found that after 2 weeks of application the concentration of luliconazole was higher at all nail layers and that luliconazole demonstrated higher mean rates of inhibition zone formation, a measurement of antifungal activity [104]. More clinical studies are needed to quantify the efficacy of luliconazole, and phase III results are expected.

Older topical azoles
Tioconazole and bifonazole are two imidazoles that have been available for over two decades for the treatment of onychomycosis. Tioconazole is sold in the UK and Europe as a 28% solution. It demonstrated modest efficacy for the treatment of onychomycosis in older studies, although recent data are lacking. In a 1985 open-label study of 27 patients treated for onychomycosis of the fingernails and toenails with tioconazole solution, six patients (22%) achieved a clinical cure at 3 months after therapy. It was noted that toenail infections responded poorly to tioconazole therapy [105].

Bifonazole, another topical imidazole, has been used in combination with 40% urea cream or paste. Urea is applied to the toenail under occlusion until the nail can be non-surgically debrided, and patients then apply bifonazole cream daily. In a multicenter study involving 692 patients with mild to moderate onychomycosis, cure rates after 4 weeks of daily bifonazole treatment were superior in the bifonazole treatment group compared with placebo at 2 weeks post treatment. However, the superior response rate was not significant at 6 months post treatment [106]. In a more recent open-label study of 10 patients with mild to moderate toenail onychomycosis, all subjects achieved mycological cure after nail debridement followed by 4 weeks of daily bifonazole treatment. Additionally, significant reduction in nail thickness was observed, suggesting that this therapy may
be useful in patients with thicker toenails that preclude the use of other topical agents [107].

**Tavaborole**

Tavaborole is another new antifungal agent and is available as a 5% solution. It is the first US Food and Drug Administration (FDA)-approved oxaborole – a new class of boron-containing antifungals that have a unique chemical structure and mechanism of action, inhibiting fungal protein synthesis by targeting fungal cytoplasmic leucyl-transfer ribonucleic acid (tRNA) synthetase. Its low molecular weight (151.9 Da) allows for excellent nail penetration compared with the older agents ciclopirox and amorolfine [108]. In addition, tavaborole retains its antifungal activity once it diffuses through keratin [108].

---

*Figure 12.46 Three cases of dermatophytoma (a,c,e) before and (b,d,f) after efinaconazole 10% topical solution.*
In two parallel randomized double-blind vehicle controlled studies in which tavaborole 5% solution was applied once daily for 48 weeks, mycological cure rates of 31.1% and 35.9% and complete cure rates of 6.5% and 9.1% were observed. The clinical success rate, defined as complete or almost completely clear nail with ≤10% involvement, was 26.2% and 27.5%. The majority of subjects achieving clinical success also had negative mycology (15.3% and 17.9% of the total number of subjects) [109].

Amorolfine
Amorolfine, a morpholine derivative, is a broad spectrum agent with activity against dermatophytes, yeasts, and molds. It acts by inhibiting delta 14 reductase and delta 7–8 isomerase, causing depletion of membrane ergosterol and accumulation of harmful sterols. It is available in Europe and Canada as a lacquer that is applied to the nail plate once or twice per week. After lacquer application, the solvent evaporates in 3–5 min, increasing the concentration of amorolfine in the film to 27% at the nail surface. In addition, the film’s occlusive properties result in nail plate hydration that then enhances the drug diffusion across the nail plate [110].

A study of 317 patients compared the efficacy of once or twice weekly application of 5% amorolfine for 6 months. Mycological cure was achieved in 71% and 76% of patients receiving once and twice weekly treatment, respectively. Complete cure was achieved in 46% and 52% of patients receiving once and twice weekly treatment, respectively [111]. However, complete cure for this study was defined as negative mycology and <10% nail involvement, perhaps accounting for the higher complete cure rates. These results were corroborated in a larger parallel study of 725 patients in which complete cure was achieved in 45% and 50% of subjects treated once and twice weekly, respectively [112]. Thus, twice a week application is not significantly superior to weekly applications.

Ciclopirox
Ciclopirox is a hydroxypyridone derivative that acts by chelation of trivalent cations such as Al^{3+} and Fe^{3+}, resulting in inhibition of metal-dependent enzymes, thereby disrupting the transport of nutrients and amino acids. Ciclopirox has broad spectrum activity against dermatophytes, yeasts, molds, and some Gram-positive and Gram-negative bacteria [113]. It is available as an 8% lacquer for the treatment of onychomycosis. Patients are instructed to apply the drug daily without removing previous layers, removing all layers only once weekly with isopropyl alcohol.

Two parallel double-blind vehicle controlled trials involving a total of 460 patients aged 18–70 with distal subungual onychomycosis caused by dermatophytes were conducted internationally to evaluate the efficacy of ciclopirox 8% lacquer. Subjects were treated daily with application of the ciclopirox lacquer to the nail plate as well as 5 mm of surrounding skin for 48 weeks and then followed for up to 24 weeks after treatment. A mycological cure rate of 29–36% and complete cure rate of 5.5–8.5% was demonstrated. Clinical success rate, defined as simultaneous negative mycology culture and KOH microscopy in addition to ≤10% nail involvement, was 6.5–12% [114]. A new formulation of 8% ciclopirox (hydroxypropyl chitosan–hydroalcoholic solution) has now replaced the previous one in several European countries [115].

Topical antifungals in development
The scope of topical treatments for onychomycosis is expanding with the development of several novel agents. K101 Nail Solution is a solution of urea, propylene glycol, and lactic acid that has demonstrated activity against T. rubrum and C. albicans. It has been suggested that K101 Nail Solution alters the osmotic properties of the fungal cell wall and cell membrane by a non-specific degradative effect [116]. This could prove advantageous in that antifungal resistance may be less likely to develop. In a placebo-controlled trial, the mycological cure rate of K101 Nail Solution after 24 weeks of treatment was 17% [117]. In a smaller study, the majority of patients reported improvement in nail appearance after 2 weeks of treatment [118].

ME1111 is a new and novel antifungal agent with potent activity against T. rubrum and T. mentagrophytes. It is the first in its class, with a mechanism of action that inhibits succinate dehydrogenase, a critical enzyme in the fungal cell respiratory process. Another distinguishing feature is its small molecular size, allowing for effective nail penetration. Given its potent activity against dermatophytes and its excellent nail penetration, it shows promising potential as a treatment for onychomycosis [119]. It is currently being investigated in several clinical trials.

A terbinfine nail solution (P-3058) has demonstrated success in two parallel dose-finding studies for the treatment of onychomycosis. Daily application of a 2%, 5%, or 10% solution was used for 24 weeks. The decrease in the affected nail area compared with baseline area of involvement was used as the efficacy endpoint. Significant results were seen for the 5% and 10% solution treatment groups at the end of treatment [120, 121]. Phase III studies are planned in the USA and Europe.

Side-effects of topical antifungals
The side-effects associated with topical agents for onychomycosis are usually mild and localized. Common adverse events reported in trials of topical agents include redness, itching, swelling, burning or stinging, blisters, pain, and ingrown toenails. Severe allergic reactions or systemic side-effects have not been reported.
**Chapter 12**

**Systemic therapies**

Oral antifungal agents have greater success rates than topical therapies for onychomycosis, but use can be complicated by drug interactions and systemic side-effects such that safe use requires periodic laboratory monitoring. Oral agents can be associated with hepatotoxicity, drug allergic reactions (erythema multiforme, drug-induced hypersensitivity syndrome, urticarial and morbilliform eruptions), taste disturbances, and even cardiac issues such as congestive heart failure. Slow nail growth in the elderly and in patients with vascular comorbidities often require several months of therapy, with high failure and recurrence rates [122].

**Terbinafine**

Terbinafine is a commonly used antifungal to treat dermatophytic onychomycosis as well as other dermatophyte infections. It is an allylamine that disrupts ergosterol synthesis by inhibiting squalene epoxidase, which prevents the conversion of squalene to lanosterol. The accumulated squalene is toxic to the fungal cell, and results in cell death [123]. While terbinafine is very active against dermatophytes, it is ineffective in vivo against non-dermatophyte molds and *Candida* spp [124]. Thus, diagnostic tests such as a fungal culture should be performed prior to initiating terbinafine therapy to confirm the presence of a dermatophyte.

Terbinafine is typically given 250 mg daily for 12 weeks for toenail onychomycosis and 6 weeks for fingernail onychomycosis. In phase III clinical studies for onychomycosis, terbinafine yielded the complete and mycological cure rates of 38% and 70%, respectively [125]. Several studies have investigated other dosing regimens, including pulse therapy of 500 mg daily for 1 week monthly for 2 months for fingernails and 4 months for toenails and intermittent therapy of 250 mg daily for 1 week every 3 months [126, 127]. These regimens have shown similar efficacy as standard dosing, likely because terbinafine can persist in the nail matrix for several months [126, 128]. Advantages of pulsed or intermittent dosing may include lower cost and fewer side-effects. Dosing in children less than 40 kg is weight based, although treatment duration is the same as for adults.

Randomized double-blind trials of oral terbinafine 250 mg daily for 12–16 weeks demonstrated superior efficacy to older agents itraconazole, fluconazole, and griseofulvin [128]. In a trial comparing continuous terbinafine therapy with intermittent itraconazole therapy, terbinafine produced a complete cure rate of 35% (vs 14%), a mycological cure rate of 46% (vs 13%), and a clinical cure rate of 42% (vs 18%). At 5-year follow-up, the clinical and mycological relapse rates for terbinafine were 21% and 23% compared with 48% and 53% for itraconazole [129]. Since these pivotal studies, terbinafine has become the treatment of choice for dermatophyte onychomycosis.

Terbinafine is generally well tolerated. Gastrointestinal complaints may occur but are usually mild. Serious side-effects including hepatotoxicity, severe cutaneous drug reactions such as drug hypersensitivity syndrome, generalized exanthematous pustulosis, toxic epidermal necrolysis, and anaphylaxis are rare. Therefore, caution should be used in patients with liver dysfunction, but the risk of liver toxicity is about 1:150 000. Many physicians periodically monitor liver enzymes, but recent data suggest that this is not always necessary [130].

**Itraconazole**

Itraconazole is a broad spectrum triazole agent with activity against dermatophytes, non-dermatophytic molds, and *Candida* spp. Like other drugs in its class, itraconazole prevents the conversion of lanosterol to ergosterol by inhibiting the cytochrome P450 enzyme 14-demethylase. Because of this, itraconazole interacts with many drugs and is contraindicated for use with HMG-CoA reductase inhibitors because of the increased risk of rhabdomyolysis and with quinidines because of the risk of ventricular arrhythmias, including torsade de points [131, 132].

Itraconazole is dosed at 200 mg daily for 6 weeks for fingernail onychomycosis and for 12 weeks for toenail onychomycosis. Alternatively, itraconazole can be given intermittently (pulse therapy) 400 mg daily for 1 week per month for 3–4 consecutive months for toenail infections and 2 months for fingernail infections [133]. Pulse therapy is considered safer than daily therapy because of the reduced risk of serious side-effects; it is also less expensive because less medication per month is required. In addition, itraconazole pulse therapy can be combined with terbinafine pulse therapy [134].

In a metaanalysis of randomized controlled trials, mycological cure rates of itraconazole averaged 59(±5)% for continuous therapy and 63(±7)% for pulsed therapy [135]. Another metaanalysis of studies comparing continuous and pulsed regimens showed average clinical cure and mycological cure rates for toenail onychomycosis at follow-up 12 months after the start of therapy of 86(±9)% and 74(±3)% for continuously dosed itraconazole at 200 mg daily for 3 months. For toenail onychomycosis treated with three pulses of itraconazole at 400 mg daily for 1 week per month, the average clinical and mycological cure rates were 82(±3)% and 77(±5)% at follow-up 12 months after the start of therapy. The cure rates were somewhat higher for fingernail onychomycosis [136].

Common side-effects of itraconazole include gastrointestinal and neurological side-effects (headaches, dizziness), and rarely hepatotoxicity and morbilliform eruptions. A serious but rare side-effect is congestive heart failure, initially reported in 58 individuals between 1992 and 2001.
and resulting in 13 deaths. It has been proposed that itraconazole has a negative inotropic effect on the myocardium, although the mechanism is unknown [137]. Thus, itraconazole should be used with caution in patients with significant cardiac risk factors or history of congestive heart failure. As with oral terbinafine, laboratory monitoring may be required in some patients [123]. Furthermore, patients who frequently take antacids for gastroesophageal reflux disease or peptic ulcers or those with achlorhydria are not the best candidates for itraconazole therapy because of the decreased absorption associated with reduced gastric acidity. Co-administration of benzodiazepines with itraconazole should also be avoided owing to the possibility of excessive sedation and airway compromise [138].

Itraconazole has been studied recently in a new formulation utilizing Meltrex® technology, which delivered 200 mg of itraconazole in a single capsule (compared with two 100-mg tablets). The phase III randomized, placebo-controlled trial showed the non-inferiority of the 200-mg capsule compared with tablets and also demonstrated a comparable safety profile. This is a more favorable formulation, as patient compliance may be improved [139].

Fluconazole

Fluconazole is a broad spectrum fungistatic bis-triazole that, like itraconazole, selectively inhibits the cytochrome P450 enzyme 14-demethylase [124]. While it is not FDA approved for the treatment of onychomycosis in the USA, fluconazole has shown excellent efficacy.

In a multicenter, double-blind, placebo-controlled study, 362 patients with mycologically confirmed onychomycosis were randomized to treatment with fluconazole, 150, 300, or 450 mg once weekly, or placebo once weekly for a maximum of 12 months. Clinical cure (completely healthy appearing nail) at the end of treatment was 28–36% and mycological cure was 47–62% [140, 141]. Clinical success was defined as a reduction of nail involvement area to <25%, and was 77–86% for toenail onychomycosis [141]. The suggested dosage of fluconazole for onychomycosis is 150 mg once weekly for 6 months for fingernails and 12 months for toenails [124].

Oral antifungals in development

Posaconazole

Posaconazole is a broad spectrum triazole not approved in Europe or the USA for the treatment of onychomycosis. As with the other azoles, posaconazole acts by inhibiting the cytochrome P450 enzyme 14-demethylase. High levels in the nail can be achieved rapidly and maintained throughout the course of treatment [142]. It is also well tolerated and has a high efficacy in vitro against dermatophytes [143].

A study found that 200 mg daily for 24 weeks is the most effective dose regimen for obtaining a complete cure (54.1%) for toenail onychomycosis and was superior to terbinafine (although differences were not statistically significant) (Table 12.3). The mycological cure rate of 70.3% was similar to that of terbinafine as well [144]. Thus, posaconazole may provide an alternative for patients unable to tolerate terbinafine or those with non-dermatophyte infections. However, posaconazole is currently used in patients with severe systemic fungal infections and therefore is not the best option for patients with onychomycosis.

VT-1161

VT-1161 is a potent and selective inhibitor of the fungal CYP51 enzyme that has shown great potential in phase II trials in the USA for the treatment of onychomycosis. It is effective against both dermatophytes and Candida species [145, 146]. A phase II study investigated the efficacy of VT-1161 for the treatment of onychomycosis in two dosing regimens. VT-1161 was administered once weekly for either 10 or 22 weeks after a 2-week dose-loading period. The study enrolled 260 patients with 25–75% target nail involvement (average 46%). The treatment success rate (≤10% involvement at week 24) was reported as 35%. Phase III studies are expected [147].

Non-surgical devices for the treatment of onychomycosis

Medical devices are increasingly important options in the treatment of onychomycosis and can be utilized as a monotherapy or coupled with topical or oral antifungal treatments. The advantage these devices offer is the ability to modify treatment duration or intensity based on the patient’s tolerance and severity of condition. Treatment application has been evaluated in several medical devices such as ultraviolet radiation, iontophoresis, and lasers; however, rigorous randomized controlled trials evaluating devices and/or combination treatment have not been published and applicability for treatment of onychomycosis is yet to be determined [148–150].

Candidates for devices are those patients who have failed previous therapies or those patients in whom systemic therapies are contraindicated owing to polypharmacy or drug interactions, as well as those patients who have difficulty applying topical medications. Patients with certain non-dermatophyte molds, such as N. dimidiatum infections, in whom there is no good alternative therapy, may also be considered ideal candidates.

Lasers

Laser therapy consists of pulses of moderate energy that are directed to specific objects in the tissue (called chromophores) via “light amplification by stimulated emission of radiation” (LASER) [151]. Targeted areas are
destroyed through heat while minimizing photothermal damage to the surrounding areas. This is the principle of selective photothermolysis that characterizes the laser–tissue interaction. Users are able to target specific chromophores by selecting the proper wavelength in the absorption spectrum of the target chromophore, causing locally confined destruction with minimal damage to the surrounding tissues. Light penetration increases with increasing wavelengths [152]. The majority of laser devices function on the deep red or near-infrared spectra (above 700 nm), thus being able to penetrate through the nail plate and the periungual tissue. Several lasers have been granted FDA marketing approval for the treatment of onychomycosis [153].

Many studies have investigated the use of lasers in the treatment of onychomycosis. A review of 22 studies showed that lasers are generally well tolerated with only mild adverse events occurring. However, the variability with which individual studies were conducted makes drawing conclusions difficult. These studies employed small sample sizes and varied in treatment regimens and efficacy endpoints. Furthermore, cure rates were inconsistently defined. Currently, there is no conclusive evidence that laser therapy is effective for onychomycosis [154].

**Types of lasers**

Since 2010, the FDA has approved seven laser devices to be used as a *cosmetic treatment* for the “temporary increase in clear nail growth in patients with onychomycosis” [155]. This clearance is based on “substantial equivalence” to predicate devices. It is noteworthy that it does not prove their efficacy in treating onychomycosis, but only their safety as more vigorous studies are needed. The FDA has suggested that evaluator binding and enclosing a detailed description of specific parameters (pulse duration, energy per pulse, repetition rate, etc.) within the trial design can all lead to more standardized results [156].

*Neodymium:yttrium–aluminum–garnet (Nd:YAG) laser* systems are the commonest laser device used in vivo for the treatment of onychomycosis at a wavelength of 1064 nm, although the 532-nm and 1320-nm wavelengths have also been tested in limited studies [157–159]. In a multipart study conducted using a Nd:YAG 1064-nm laser, efficacy against three nail pathogens (*T. rubrum*, *E. floccosum*, and *Scytalidium*) was evaluated both in vitro and in vivo. No inhibition was seen after treatment of fungal colonies and suspensions. In vivo treatment of toenails also did not show significant clinical response [160]. In a recent prospective randomized controlled trial, 82 toenails with confirmed onychomycosis were treated four times at 4–6-week intervals with either a 1064-nm-Nd:YAG laser or no laser treatment. Negative culture and histology was the primary endpoint, and clinical improvement was the secondary endpoint. Neither of these was achieved. Two larger clinical studies are currently ongoing into laser use in patients with diabetes and onychomycosis [161].

**Diode lasers**

Diode lasers operate at temperatures that are safe for human tissues, but manifest lethal effects on fungi at near-infrared light wavelengths (870 and 930 nm) [162]. At 405 nm a diode laser presents direct fungicidal activity and at 635 nm it stimulates a natural immune response [163]. Sullivan et al. [163] combined the effects of two different wavelengths to provide treatment in 1600 affected nails of 320 patients. Patients’ nails were first subjected to debridement and were additionally treated with topical antifungal agents. Investigators reported high response rates but did not use stringent definitions of cure [163]. Previous, though smaller, studies have reported similar findings.

**Ablative lasers**

Ablative lasers include carbon dioxide and erbium (Er) lasers. They are being studied as adjuvants to topical therapies for onychomycosis, as they can facilitate drug delivery through the nail plate by increasing permeability [164]. A few small studies have been done and have shown promising results, although more rigorous studies are needed. In a small study of nine patients and 20 affected toenails, the Er:YAG laser was used in five treatments over 12 weeks combined with twice weekly application of amorolfin 5% lacquer and compared with amorolfin 5% twice weekly alone. Most laser-treated toenails showed improvement: the mean severity score decrease was significantly higher in laser-treated nails and the rate of negative mycological examination at week 24 was significantly lower in the laser-treated group [164]. A larger trial is ongoing [165]. In a small unblinded study of 24 patients with onychomycosis treated with a fractional CO2 laser and topical antifungal cream, the authors report 92% clinical response and 50% complete response defined by negative mycology and 0% nail involvement [166].

**Lasers in combination therapy**

The advantage of combining therapies allows for compensation of any limitations treatments might have in monotherapy. Combining topical drugs with lasers may increase nail penetration and allow higher concentrations of the drug to reach the site of infection. Specific combinations of topical drugs and lasers have not received FDA approval as of yet. The FDA has suggested that the use of proper controls (e.g. individual treatments used in monotherapy) when evaluating combinations is necessary to standardize results [155]. Pharmacodynamics and pharmacokinetics are highly dependent on the specific combinations created.
Fungal (Onychomycosis) and Other Infections Involving the Nail Apparatus

Adverse events
Adverse events caused by the use of lasers to treat onychomycosis are usually mild and tend to be associated with the high-energy Nd:YAG lasers [161, 162]. Painful onycholysis has been reported after treatment with Nd:YAG lasers [164]. Pain and numbness are possible with other lasers as well. A potentially serious complication of laser treatment is non-healing wounds in patients with diabetes. In a case report, Nd:YAG treatment for onychomycosis in a patient with diabetic neuropathy resulted in osteomyelitis and toe amputations [167]. Thus, patients with diabetic neuropathy may not be good candidates for laser therapy as lack of pain sensation may lead to overtreatment and eventual necrosis.

Photodynamic therapy
Photodynamic therapy (PDT) utilizes a phototoxic reaction that occurs following topical application of a photosensitizing prodrug. After application of the photosensitizing agent, the affected toenail is irradiated with light at a specific wavelength of the visible spectrum, generating chemical reactions that convert porphyrins to protoporphyrins and reactive oxygen species; this destroys fungal hyphae and inactivates fungal spores. Reactive oxygen species, especially singlet oxygen, lead to both apoptosis and necrosis of target cells. Moreover, PDT acts as a biological response modifier by induction of innate and adaptive host immune responses [168, 169].

There are several types of photosensitizers used in PDT, such as 5-aminolevulinic acid (5-ALA), methyl aminolevulinate, and methylene blue (MB), that have been evaluated for their potential in treating onychomycosis [170–172]. The majority of PDT studies for onychomycosis have used red light for irradiation, as red light is used primarily outside of the USA. However, in vitro studies show that blue light also has potential use in PDT [173]. Indeed, the majority of other uses for PDT using ALA as the photosensitizer employ blue light irradiation and blue light is used for PDT in the USA.

ALA-PDT was used to treat T. rubrum onychomycosis in a single-center open trial of 30 patients and showed cure rates of 43.4% 12 months post treatment and 36.6% 18 months post treatment. Patients received three treatments at 2-week intervals with red light after an incubation time of 3h with 5-ALA. Cure was defined as completely clear nail without any signs of onychomycosis or <10% involvement in addition to negative mycological examination [174].

In an open-label controlled clinical trial of 22 subjects using MB-PDT for the treatment of onychomycosis, patients with confirmed T. rubrum infections were treated with red light PDT over 6 months with 15 days between treatments. The authors report that mycological cure occurred in all patients, although clinical response rates were superior in patients with mild-to-moderate distal–lateral subungual onychomycosis (100%) compared with patients with severe distal–lateral subungual onychomycosis (63.3%) [169]. This corroborated the results of an earlier, smaller study [175].

Adverse events
Common adverse events seen in patients treated with ALA-PDT were burning sensations and pain. In many cases, pain during treatment led to interruption of the procedure for 5–10 min. In addition, moderate but transient local phototoxic reactions were observed in most patients in a study using ALA-PDT, including signs of erythema, edema, and blistering [169].

Iontophoresis
Iontophoresis is a non-invasive technique that uses low-intensity electrical current to increase the penetration of polar and high-molecular-weight molecules across biological membranes [176]. In iontophoresis, drug transport by the tissue occurs mainly through the skin appendages such as sweat glands and hair follicles, which work as alternative pathways to allow passage of macromolecules and polar molecules into the body [177–179]. One challenge when using topical medication is maintaining a sufficient concentration of the antifungal drug in the nail plate and underlying tissue. The goal of iontophoresis is to increase the quantity of terbinafine (or other topical antifungal agents) accumulated in the nail plate via uptake from a passive source, which works as a reservoir that drops the drug into the nail plate and matrix.

Several reports using iontophoresis for nail drug delivery in vitro have been documented. The first clinical study was reported in 2009, when 38 patients were randomly divided into two groups [180]. The results show 40% of patients having healthy toenail growth of more than 1–5 mm in the group that used terbinafine gel in conjunction with iontophoresis compared with 11% in the group that used terbinafine gel alone; the percentage of patients having fungal elements (KOH examination) in nail specimens was 16% in the group with terbinafine gel and iontophoresis versus 53% in the group without iontophoresis.

Adverse events
Iontophoresis is well tolerated overall, although patients frequently experience a tingling sensation during treatment. Skin irritation can also occur, including development of erythema, vesicles, and associated discomfort [181]. Rarely, patients may suffer thermal burns because of minor skin injuries or skin contact with metal items. These side-effects do not typically require interruptions of treatment.
Surgical treatments

Topical and oral antifungal treatments for onychomycosis do not achieve a complete mycological cure in all patients. Surgical intervention may be helpful in cases that are particularly resistant to topical and systemic treatment, especially when severe onycholysis, dermatophytomas, longitudinal yellow streaks are present and in those patients with infection involving the lateral sulcus of the nail plate. These cases are difficult to treat because of the impenetrability by the oral antifungal agents. Surgical treatments can be divided into simple debridement or chemical or surgical avulsion.

Debridement

Debridement to the most proximal edge of infection increases the mycological cure rate and may shorten the duration of systemic therapy [182] (Box 12.2). In some patients, it may be helpful to remove infected keratin and debris from an onychomycotic nail mechanically (debridement or drilling), chemically (urea), or surgically. Debridement starts with the mycological sampling, but can also add esthetic value as well as eliminate nail bed hyperkeratosis [183]. The decrease in fungal mass also adds to successful treatment, and can be adjunct therapy for many patients [183–185].

Mechanical debridement is well tolerated and generally does not require local anesthesia. It is performed by removing the grossly infected portions of the involved toenails that are discolored, lytic, thickened, or deformed [185]. This procedure improves the appearance of the nail by reducing hypertrophy and also reduces pain from pressure of a thickened nail in the shoe. This can be done with a heavy-duty nail clipper. Since this is a non-invasive procedure, it may also be helpful in patients with advanced peripheral vascular disease and diabetes, which are conditions that are often associated with decreased cure rates from conventional therapies. A curette may be used to remove the subungual debris (hyponychial keratin) from the nail bed, as it is very rich in fungal filaments.

In a study, 55 patients with proven dermatophyte pedal onychomycosis were randomly allocated to either nail debridement alone or debridement plus application of topical ciclopirox. After a 10-month follow-up, patients in the antifungal group improved statistically significantly more than those in the debridement alone group, and displayed over 75% mycological cure rate [186].

Others have replicated similar results demonstrating the benefit of debridement used in conjunction with topical antifungal agents [187].

Chemical avulsion (Figs 12.47, 12.48)

Chemical avulsion can be accomplished with 40% urea and is a well-established practice [188, 189]. It is a painless method that may be used in any type of onychomycosis.

Box 12.2  Indications for nail debridement

- Thick nail plate
- Significant nail bed hyperkeratosis
- Lateral nail involvement
- Significant onycholysis

Figure 12.47 Urea chemical avulsion.

Figure 12.48 Urea chemical avulsion before and after removal of the affected nail portions.
as long as the part of the nail plate underneath the proximal fold is not affected, and is a painless alternative to surgical avulsion. The main advantage of this technique is that it is a “selective avulsion,” acting only on the infected keratin. Urea dissolves the bonds between the nail bed and the nail plate, and also softens the nail plate. The paronychium is protected with thick adhesive tape in order to prevent chemical irritation of the soft tissues. The urea paste is liberally applied onto the plate [190]. The patient is instructed to keep the nail occluded and to avoid wetting the treated area, as inadequate occlusion and/or immersion are causes for failure [191]. After 1 week of occlusion, the infected part of the nail is removed with a nail clipper without pain. The hyperkeratosis on the nail bed should be gently scraped away with a curette and then vigorously rubbed with wet gauze to remove all subungual debris, until the bed is clean. If the nail was very thick it might be necessary to repeat the procedure for an extra week. If left too long the urea is no more selective and will detach the whole plate from the bed.

**Surgical avulsion** (Figs 12.49–12.52)

Surgical avulsion requires local anesthesia, sterile technique, and controlled hemostasis.

It is performed in the same manner as the distal approach of total nail avulsion, but restricted to a portion of the nail plate. The portion of nail plate to be avulsed is freed from its bed attachment by inserting the elevator under the plate. The latter is sectioned to the desired size with fine scissors or fine nail clippers to avoid inducing any lateral onycholysis. Surgical avulsion may be used to improve the efficacy of topically applied antifungals [192–194]. Partial avulsion may be helpful in treating some types of onychomycosis (i.e. longitudinal streaks, lateral disease, dermatophytoma, onycholysis, and onychomycosis caused by molds) [195–197]. The advantage of partial surgical nail avulsion is that a large portion of the normal nail plate (which still exerts a pressure on the underlying soft tissues) remains, reducing the risk of distal embedding.
Combination therapy with nail drilling

Nail drilling can enhance drug delivery of topical treatments by creating mechanical passages in the nail plate for topical drugs to enter [198, 199]. There is a high risk of oral drugs confounding medical device results; therefore, the FDA does not support the use of mechanical avulsions or nail drilling with oral antifungal treatment [155].

The FDA has cautioned against the use of debridement since it can “artificially” increase the percentage of clear nail and recommends debridement to be used as a functional improvement in treatment regimens [155]. An open comparative study has evaluated the combination of nail drilling with oral and topically administered terbinafine in patients with mild to moderate onychomycosis (n = 98) [198]. Three treatment groups were used: nail drilling combined with 250 mg terbinafine (daily for 2 weeks) and terbinafine spray (1% twice daily for 6 months) (group 1), nail drilling combined with terbinafine spray (1% twice daily for 6 months) (group 2), and terbinafine spray (1% twice daily for 6 months) only (group 3) [198]. In every intervention two horizontal lines (1.8 mm) were drilled (2 mm apart) at the border between the healthy and diseased part of the nail [198]. There were significant improvements in the amount of clear nail in group 1 (combination of three therapies) compared with group 3 (topical alone) in patients with 51–75% nail involvement (p = 0.038). The addition of oral terbinafine did not significantly increase the efficacy of the topical terbinafine and nail drilling combination (p = 0.145). Most patients (82%) did not experience pain when terbinafine (administered in a spray or tablet) was combined with nail drilling. The highest reported level of pain was 4 on a scale of 10 [198].

Topical treatments have been combined with nail drilling in complicated cases (e.g., patients with diabetes) with some success. A nail driller (Hadewe SB-40; Hainholzer Dental-Werkstatt, Hannover, Germany) using an electric grinder combined with ketoconazole, terbinafine hydrochloride, bifonazole, clotrimazole, or butenafine hydrochloride was used to treat onychomycosis in patients with diabetes (n = 23) [199]. There were four patients who were cured of SWO after treatment, with application frequency dependent on the topical drug used (6 months to 1 year). A significant improvement in the scoring clinical index for onychomycosis was found after 6 months in patients with distal-lateral subungual onychomycosis.

Conclusions

Therapy of onychomycosis has improved significantly with the introduction of oral terbinafine and itraconazole more than two decades ago, when most patients with onychomycosis went untreated or underwent painful nail avulsion. Subsequently, there have been exciting developments in both topical antifungal therapy and devices specifically designed to cure patients with fungal nail infections. With current technology and medications, most patients with dermatophyte onychomycosis can be cured. However, there are still gaps in the treatment of nail infections caused by non-dermatophyte molds, and in dermatophyte infections recalcitrant to oral agents.

Management of special situations in onychomycosis

In primary onycholysis of the great toenails, associated with dermatophyte invasion, measures should be taken to relieve the effects of pressure and trauma, such as the provision of fitted shoes, padding, or toe shields. Daily topical treatment with antifungal therapy and repeated trimming of the non-adherent portion of nails should be started.

Nails affected by SWO caused by dermatophytes should be abraded after confirming the diagnosis by taking scrapings. When the culture is negative, a tangential piece of the nail plate, using the shave excision technique, or a 3-mm punch biopsy of the nail plate is taken for histopathology. This will avoid unnecessary systemic therapy since topical treatments such as amorolfine or ciclopirox alone are effective. Coexistence of white superficial onychomycosis and DLSO or the striate form of superficial onychomycosis is an indication for oral therapy. In the elderly or those with isolated lesser toenail involvement, treatment may be unnecessary and control of nail thickening by chiropody may be the best alternative. The 40% urea–1% bifonazole ointment may be used, combining the advantages of considerable nail softening with antymycotic action on the infectious keratotic debris from under the nail. It is wise to avoid salicylic acid in combination with urea if there is peripheral circulatory insufficiency.
Non-dermatophyte mold onychomycosis

Assuming that the pathogenic role of mold fungi isolated from the affected nails has been confirmed using the criteria discussed previously, three patterns of infection must be considered.

- SWO caused by Acremonium, Aspergillus, or Fusarium spp.
- DLSO caused by S. brevicaulis and certain other molds such as Pyrenochaeta unguis-hominis [200], N. dimidiatum previously known as Hendersonula toruloidea [201, 202] (Fig. 12.9), or Nattrassia mangiferae and N. hyalinum [203].
- Proximal subungual onychomycosis due to Fusarium spp.

SWO caused by non-dermatophytes may respond to abrasion of the nail surface followed by topical therapy with imidazole agents, particularly those with better in vitro activity against mold fungi such as econazole, clotrimazole, 28% tioconazole, amorolfine, 8% ciclopirox nail lacquer; 10% glutaraldehyde may also be effective. However, topical therapy may be useful for the other categories of early or mild infection. Repeated chemical removal of the nails, followed by local applications of keratolytics and antifungal agents, may also be tried. Although there is evidence that some cases of onychomycosis due to mold fungi respond to single oral antifungal treatment such as itraconazole or terbinafine [199], the response is not predictable and some combination of nail removal and oral/topical therapy is usually necessary. Fusarium and Neoscytalidium infections of the nail plate are also difficult to treat and a combination approach as well as nail removal is often used with varying degrees of success. There is also evidence that the clinical progress during the treatment of nails containing some mold fungi as well as the dermatophytes is determined by the response of the dermatophytes alone [204].

Candida onychomycosis

Nail dystrophy caused by Candida can be treated with oral itraconazole or fluconazole, or chemical removal followed by local antifungal treatment. If these methods are unsuccessful, combined avulsion and chemotherapy should be used. In chronic mucocutaneous candidiasis, the daily dose of itraconazole may have to be increased to 200 mg daily. When remission is induced, treatment should be stopped. Resistance to this drug has only rarely been recorded.

Onycholysis with Candida colonization

This variety often coexists with bacterial infection (Pseudomonas or Proteus). The patient should be advised to wear thin cotton gloves, which are regularly cleaned, under rubber gloves used for all wet work and to avoid excessive immersion in hot water, even when wearing protective gloves. After hand washing, the nail fold area must be dried carefully. In some cases the use of a hairdryer is recommended to keep the nail plate–nail bed space as dry as possible. The nail plate has to be trimmed as far back as possible: if the patient is anxious, local anesthesia may be required. Scissors are used to separate the nail plate proximal to the onycholytic area; then the nail bed should be debrided with a piece of gauze wrapped around a stick. Four percent thymol in chloroform or 15% sulfacetamide in 70% ethyl alcohol may be applied twice daily to the space to suppress growth of Candida and Pseudomonas. The specific antifungal solutions (i.e. miconazole, clotrimazole) may supplement this treatment. Thorough trimming should be repeated at intervals of 4 weeks until the nail reattaches. “Green nails” deserve the same treatment despite good but inconsistent results obtained by Zaias [205] with Clorox®, diluted 1 in 4, a few drops being applied three times a day. Polymyxin B is no longer used for Pseudomonas infections; brushing the nail area with 1–2% acetic acid is an alternative method. The patient should be warned against cleaning with a nail file or orange wood stick under an area of onycholysis as this may increase the split.

Removal of organisms in patients with onycholysis may improve the appearance of the nails but will not produce healing of the split between nail plate and nail bed.

Chronic Candida paronychia

As in all varieties of paronychia, protection of the hands from water (as for onycholysis) is an indispensable part of management. Topical antifungal agents active against Candida must be applied to the groove between the nail plate and the proximal fold at least twice daily. Solution formulations of these drugs are much more effective than creams or ointments for paronychia. Treatment usually has to be continued for at least 3 months and until the nail fold lies flat against the nail plate. If there are frequent acute episodes, combined treatment using intraleosional or systemic steroid therapy and systemic antibiotics such as erythromycin 1 g daily or tetracycline 1 g daily for 1 week may be useful. Systemic antifungal therapy works in this condition but is no more efficacious than topical treatment. For instance, fluconazole (50 mg/day) was effective in the management of chronic Candida paronychia [206].

Treatment should not be considered complete until the cuticle has regrown. Reattachment of the proximal nail fold to the nail can be encouraged by dabbing the groove with a toothpick dipped into 80% phenol. All the affected areas of the nail plate should be clipped away or abraded. An alternative is the use ofazole antifungal lotions applied along the nail fold and allowed to seep under this area. Chemical removal is an alternative for completely dystrophic nails.
Other fungal infections

Sporotrichosis

Sporotrichosis (Figs 12.53, 12.54) is a subcutaneous fungal infection caused by the dimorphic yeasts of the genus *Sporothrix*, such as *S. schenckii* or *S. brasiliensis*. The infection follows implantation of the organism, which is found in the environment in subtropical and tropical countries. The primary site of infection is commonly located on an exposed site and the nail fold is often involved. The area becomes edematous and discharges pus and serous fluid. Secondary lesions may develop subsequently along the course of draining lymphatics. The best method of diagnosis is by culture, although biopsy may reveal round or oval yeast or asteroid bodies – yeast surrounded by a refractile eosinophilic halo. The usual treatment is a saturated solution of potassium iodine; oral itraconazole or terbinafine are alternatives.

Other deep mycoses

Patients with chromoblastomycosis and coccidioidomycosis may present with a clinical picture of DLSO resulting from the invasion of the undersurface of the nail by the deep mycotic agent [35].

Infection in other chapters

Please see the following chapters for other types of infection that also affect the nail apparatus.

- Chapter 10: impetigo, *Veillonella*, nursery staphylococcal infection, blistering distal dactylitis
- Chapter 18: tetanus, erysipelas, *Mycobacterium marinum*, tularemia, milker’s nodule

References

384 Chapter 12


Chapter 12


Chapter 13

Bacterial, Viral, and Other Infections

Archana Singal¹ and Bertrand Richert²

¹ Department of Dermatology and STD, University College of Medical Sciences, Delhi, India
² Department of Dermatology, Brugmann, St Pierre and Queen Fabiola University Hospitals, Université Libre de Bruxelles, Belgium

Introduction

Many viral, bacterial, and parasitic diseases are likely to involve the nail unit (Box 13.1).

Viral infections

Herpes simplex

Distal digital herpes simplex virus (HSV) infections (Figs 13.1–13.5), caused by HSV type 1 or 2, may affect the terminal phalanx as herpetic whitlows or start as an acute, intensely painful paronychia. Recurrent forms are generally less severe and have a milder clinical course than the initial infection. Medical personnel and dentists are at a higher risk of acquiring the infection because of direct contact with the patient with infection.

After an incubation period of 3–7 days during which local tenderness, erythema, and swelling may develop, a crop of vesicles appears at the portal of entry into the skin. The vesicles typically are distributed around the paronychium and on the volar digital skin and somewhat resemble a pyogenic infection of the fingertip. An acutely painful whitlow may develop and extend under the distal free edge of the nail and into the nail bed. A distinct predilection for the thumb and index finger was noted by La Rossa and Hamilton [1] but any finger may be involved. Several fingers may be affected together. Recurrent herpetic whitlow of the great toe has been reported in a 9‐month‐old healthy infant [2]. For 1–14 days the vesicles gradually increase in size, often coalescing into

Box 13.1 Infective diseases that may involve nail unit

- **Viral**: herpes simplex, herpes zoster, human papillomavirus, HIV, hand–foot–mouth disease, orf, molluscum contagiosum, chikungunya
- **Bacterial**: acute paronychia, anthrax, syphilis, gonorrhea, pinta, cutaneous diphtheria
- **Mycobacterial**: tuberculosis, leprosy, other mycobacterial infections
- **Infestations**: scabies, pediculosis, tungiasis, subungual myiasis, trichinosis
- **Parasitic**: leishmaniasis, malaria, cutaneous larva migrans
- **Miscellaneous**: Kawasaki disease
large, honeycomb-like bullae. New crops of lesions may appear during this time. Vesicular fluid is clear early in the disease but may become turbid, seropurulent, or even hemorrhagic in the later stages. At times, the pale yellow color of the vesicles will suggest pyogenic infection, yet frank pus is not usually obtained. Patients complain of tenderness and severe throbbing in the affected digit. Coexisting primary herpetic infections of
the mouth and fingernails suggest autoinoculation of the virus into the nail tissues as a result of nail biting [3] or finger sucking [4]. We have seen coexisting primary herpetic infection of the penis and the index finger.

Radiating pain along the C7 distribution is sometimes noted and may predict the onset of recurrent herpetic whitlows. Lymphangitis is almost always seen in periungual herpes simplex and may even precede the vesicles by 1 or 2 days. It usually starts from the wrist and extends to the axilla with enlarged and tender lymph nodes.

Numbness and hypoesthesia following the acute episode have been observed [4]. Persistent lymphedema may also occur. Superinfection with bacteria such as *Staphylococcus aureus* and streptococci may occur. HSV-2 meningitis has been reported in a 7-year-old boy following viral dissemination from a herpetic whitlow [5].

The diagnosis of herpetic infection can be made readily by cytological examination. Tzanck smears obtained from the margin of the vesicles show multinucleated “balloon” giant cells. Characteristically, the nuclei of HSV-infected cells appear steel blue and homogeneous. Viral culture is confirmatory and is usually positive within 24–48 h. Histopathology is usually not performed for periungual herpes simplex. However, herpes viruses may be seen on electron microscopy of blister fluid. Monoclonal antibodies or polymerase chain reaction (PCR) allows confirmation of the diagnosis by immunofluorescence and also differentiation of type 1 from type 2 HSV.

In patients with AIDS, recurrent herpes is severe and persistent. Herpes may be ulcerated [6], destructive [7], or necrotic [8]. Chronic herpetic whitlow may be the first manifestation of AIDS [9].

**Differential diagnosis**

It is important to exclude primary or recurrent herpes simplex infection in the differential diagnosis of every finger infection. The typical morphology of the lesions, disproportionately intense pain, absence of pus in the confluent, multiloculated vesiculopustular lesions, and the lack of increased tension in the finger pulp aid in distinguishing this slow-healing infection from a bacterial infection or paronychia [1].

Herpetic paronychia-like infection due to *Mycobacterium marinum* has been reported [10] (Fig. 13.6).

Herpes zoster infections, which may affect the proximal nail fold like herpes simplex, also involve the entire sensory dermatome. The pustules of primary cutaneous *Neisseria gonorrhoeae* infection may resemble herpes simplex on the rare occasion when it occurs on the finger. The diagnosis is established by Gram stain and bacteriological culture.

**Treatment**

Treatment is primarily aimed at symptomatic relief and avoidance of secondary infection. This is a preventable infection. Gloves should always be worn on both hands for procedures such as intubation, removal of dentures, or providing oral care [10], despite the additional costs involved [11]. Limb elevation, analgesia, and rest to the affected part may ease pain. Surgical drainage should be avoided for high potential of bacterial superinfection. While aciclovir or valaciclovir may ease the symptoms of the acute episode, a single course will not affect the chances of relapse. Continuous oral aciclovir may prevent frequent relapses in patients with recurrent herpes simplex infections, but use of this regimen may lead to drug resistance.

**Herpes zoster**

Herpes zoster (Fig. 13.7) around the nail is rare unless that particular dermatome is involved, when grouped vesicles may be seen around the proximal nail fold. Nail bed involvement is particularly painful and leaves small subungual roundish hemorrhagic spots slowly growing out with the nail. Herpes zoster may produce transverse leukonychia by a uniform but temporary disturbance in the normal activity of fingernail matrix, causing abnormal keratinization [12]. Stained Tzanck smears reveal multinucleated epidermal cells that do not allow differentiation from herpes simplex. In AIDS, herpes zoster lesions are often verrucous. Treatment requires institution of oral aciclovir or valaciclovir.

**Human papillomavirus**

Human papillomavirus (HPV) types 1, 2, and 4 are most common etiological agents for verruca vulgaris, the common wart. Periungual and subungual warts involve fingernails more than the toenails. They are often associated with low cure rates and a high recurrence rate. Intraleisional bleomycin, CO₂, and pulsed dye laser have been reported to be effective.
**Human immunodeficiency virus**

HIV infection is associated with certain nail manifestations more often, such as proximal subungual onychomycosis, candidal onychomycosis involving multiple nails, and diffuse nail pigmentation.

**Hand–foot–mouth disease**

During fall 2008, an outbreak of hand–foot–mouth disease (HFMD) with onychomadesis as a common feature occurred in Finland. An unusual enterovirus type, coxsackie virus A6 (CVA6), was identified as a new and major cause of the epidemic [13]. In the fall of 2009, an outbreak occurred in a Spanish nursery followed by onychomadesis about 36–39 days later. Twelve out of 17 children developed nail shedding. Enterovirus was detected in stool samples from eight of the 17 (47%). However, enterovirus serotype coxsackie virus B1 was identified in only three children [14]. The epidemiological results of this study confirmed onychomadesis as a complication in HFMD. In addition to self-limiting onychomadesis, occurrence of Beau’s lines and nail plate discoloration has also been reported from across the world (Fig. 13.8). Recently, a study of nail changes from China revealed onychomadesis and nail loss in 56 of 273 children with HFMD aged less than 5 years. Onychomadesis occurred 1–2 months after onset of HFMD and involved multiple nails. In 16% of these children, all finger and toenails were affected. The nail changes resolved spontaneously without specific treatment in all cases within 8 weeks [15].

**Orf**

Orf, also known as “contagious eczema,” is an uncommon zoonotic disease caused by a double-stranded DNA virus (genus *Parapoxvirus*) contracted from direct or indirect contact with infected sheep and goats [16]. The infection is most commonly encountered in veterinarians, butchers, and sheep farmers. It presents usually as a solitary (sometimes multiple) nodular lesion on the dorsum of the thumb or fingers and involves the nail folds (Fig. 13.9). After an incubation period of 3–7 days, the asymptomatic papular lesion evolves into an iris or target-shaped lesion with a central red nodule surrounded by a pale circle and an erythematous exterior margin [17].

Diagnosis is based on history and clinical examination. Laboratory investigations such as histology, electron microscopy, viral culture, and PCR may be used to confirm the diagnosis. Dermoscopic findings in orf lesions have been described in the form of a central nodule with ulceration surrounded by white structureless areas with white shiny streaks, an outer ring of dotted and hairpin vessels, and fine peripheral scales [18]. No specific therapy other than supportive treatment in the form of wet dressing and topical antibiotics is recommended because orf lesions heal spontaneously with little or no scarring after about 6 weeks and provide lifelong immunity.
Molluscum contagiosum

Molluscum contagiosum (MC) is a common viral skin infection of childhood caused by a DNA poxvirus, the molluscum contagiosum virus (MCV), and typically affects the face, trunk, and arms. The infection may be transmitted by direct skin contact, by fomites, by autoinoculation by scratching, and by sexual transmission in adults. Presence of MC lesions in relation to the nail unit is extremely rare. It has been described once in a female dermatologist presenting with a subungual mass under the distal end of the nail plate, in the middle finger of the dominant right hand. Excision biopsy revealed the presence of characteristic intracytoplasmic hyaline eosinophilic inclusion bodies (Henderson–Paterson bodies) of MCV [19]. A small swelling in relation to the proximal nail fold in a female pediatrician has also been seen (Fig. 13.10). Shave biopsy revealed classical features of MC (Fig. 13.11). The lesion was curetted under local anesthesia and had healed without scarring at 6 weeks follow-up (Fig. 13.12). In both of these cases there was a possibility of acquiring MCV during handling of infected patients.

Chikungunya

Chikungunya is a reemerging viral infection prevalent in Africa, Asia, and the Indian subcontinent. The disease is caused by an RNA virus that belongs to the Alphavirus genus of the family Togaviridae and is transmitted to humans by infected mosquitoes. The disease is characterized by fever, muscle and joint pain, and skin rash. The rash is generalized maculopapular in the majority. Another notable cutaneous manifestation is the presence of striking nose pigmentation (nose chick sign) and the occurrence of targetoid, toxic epidermal necrolysis-like, and purpuric lesions. Onychomadesis, black lunula, and subungual hemorrhage have also been reported along with skin lesions [20]. In addition, isolated diffuse pigmentation of the nail plate has been noted (Fig. 13.13) without any other skin lesions in patients with chikungunya. The pigmentation tends to persist for a few months following subsidence of the fever.
Bacterial infections

Acute paronychia

Acute bacterial paronychia is the most common acutely painful hand infection, involving fingernails more often than toenails. Women are affected more often than men and usually a single nail is involved. Patients with artificial nails are at a higher risk of developing acute paronychia as they are known to harbor large numbers of bacteria that are inaccessible to routine hand hygiene practices [21]. Trauma to the nail folds by nail biting, removing hang nails, and overzealous manicure are the common predisposing factors. Thumb sucking and nail picking have been implicated in young children (Fig. 13.14). The most common causes include *S. aureus*, streptococci, *Pseudomonas*, and Gram-negative bacteria [22, 23]. Treatment includes elimination of the predisposing factors, warm soaks, and a topical antibiotic in mild cases and systemic antibiotics in severe cases. Surgical drainage of pus with an 18-gauge needle or a no. 11 scalpel blade provides instant pain relief. If left untreated, complications such as subungual abscess formation, felon, tenosynovitis, and, rarely, osteomyelitis of the underlying phalangeal bone may ensue. For *Pseudomonas* infection, topical treatment includes twice daily application of 2% sodium hypochlorite solution or 2% acetic acid to the nail bed after cutting off the...
detached nail plate. Topical antibiotics such as nadifloxacin, ciprofloxacin, polymyxin B, and gentamicin have also been used with success. Oral quinolones (ciprofloxacin) for 2–3 weeks has been advocated in patients who prefer oral therapy.

**Anthrax of the finger and hand**

Cutaneous anthrax is the most common form of anthrax infection. It is caused by *Bacillus anthracis* and is transmitted by direct contact with spores originating from hoofed animals, hides, and surrounding soil. Endemic regions include the Middle East, especially Turkey [24]. After 1–7 days, rapidly enlarging painless red papules form on exposed parts—hands and fingers (>50%) or face—that ulcerate in the center to form a black eschar, which is often associated with intense local edema and regional lymphadenopathy [24, 25]. Diagnosis is by the demonstration of Gram-positive capsulated bacilli in a tissue smear and on histology. Treatment includes penicillin and surgical debridement in some cases.

**Gonorrhea**

The hallmark of disseminated gonococcemia is the appearance of skin lesions (Fig. 13.15) [26]. The most common is a vesicopustule that occurs juxtaarticularly over the extensor surfaces of the hands, dorsal surfaces of the toes, and around the nails. Hemorrhagic bullae occur in smaller numbers but in the same area. The third most common dermatological manifestation is the appearance of focal petechiae over the digits or the medial aspect of the ankles. Primary extragenital cutaneous gonorrhea acquired sexually is extremely rare [27]. It presents with a fingertip abscess extending under the nail plate with peripheral erythema from a pustular lesion. The diagnosis of gonococcal skin infection is often not entertained until the unexpected findings on the Gram stain prompt further questions and culture.

Histopathology shows leukocytoclastic vasculitis with endothelial swelling, fibrinoid degeneration of vessel walls, extravasated erythrocytes, and intraepidermal pustules that form from spongiform pustules.

**Syphilis**

Chancres of the fingers (due to occupational infection or sexual contact) may present as periungual erosion or ulceration. Sometimes the nail bed may be involved as in the syphilitic whitlow of Hutchinson, a paronychia, or it may resemble a pyogenic granuloma (Figs 13.16–13.19). A crusty ulceration covering the free edge of the nail in a half-moon shape or developing in one of the lateral nail folds has been reported. In this location chancres are usually painful and have a more chronic clinical course than elsewhere. Regional lymphadenopathy accompanies the primary lesion: chancres of the fingers are associated with painless, unilateral, epitrochlear, and/or axillary nodes. The affected lymph nodes are discretely enlarged, hard, and non-suppurating.
Primary syphilis of the fingers accounted for 14% of extragenital chancres according to Starzycki [28], who reported six cases. Of these, two had chancres on both their fingers and genitals resulting from sexual foreplay. Primary syphilis with exudative ulcers of the middle finger and one of the little finger of the right hand has been reported with an axillary, firm, painless lymph node [29]. A case of primary syphilis with multiple chancres and porphyria cutanea tarda in a HIV-infected patient is unique [30]. Biopsy from a 4-month-old granulating ulcer was undertaken along with nail extraction in a 33-year-old woman with a suspected diagnosis of refractory paronychia. In view of her sexual partner’s history of treatment for syphilis, reexamination of original tissue tested positive for syphilis on PCR and immunohistochemistry. Silver staining revealed large numbers of syphilis bacteria. In addition, positive serology confirmed the diagnosis of extragenital chancre [31].

In the secondary stage, the nail changes may be divided into two main groups: in the first group, the changes due to the involvement of the matrix seem to be confined to the nails themselves; in the second group, the changes are those in which the nail abnormalities are a consequence of some inflammatory condition of the peri- and subungual tissues and are without specific characteristics.

Various forms of “dry” onychia have been described: unusual brittleness with a tendency to splitting and fissuring (“onyxis craquelé”), onycholysis, pitting with a linear arrangement of the pits from the root forwards, and elkonyxis in the lunula region. Beau’s lines may be seen, sometimes latent onychomadesis appears, and, rarely, there is total nail loss. The whole nail plate may become dull, dry, and thickened with a distinct line of demarcation between the affected and the distal portions which retain polish and color, but a wedge-like thickening of the free end has been described.

Onychogryphosis may occur on the toenails. Dark or brownish pigmentation of the nail may involve the nail plate entirely or as longitudinal pigmented streaks [32]. The very rare amber-colored nail plates resembling false nails were considered by Degos [33] to be a characteristic change of late syphilis. Pigmentation of the nail occurring over papules in the nail bed [34] is seen in the second group of syphilitic nails. The nail lesions are secondary to local inflammatory disturbances.

Milian’s lilac arch [35], located at the distal nail bed, is no longer considered to be a manifestation of syphilis. It probably corresponds to a prominent onychodermal band [36]. The “isolated papule of the nail bed” [37] occurs at the time of the exanthem. A pea- to bean-sized patch appears under the normally transparent nail. At first the patch is intensely red, later yellow. The nail plate becomes thinned and fractured at this spot. This condition was said to be always limited to one finger.
In fact, nearly all the fingernails may be involved [34]. In the moist forms several nails may be affected, but often only one is involved such as the thumb or the great toe. The lesion begins with erythema, swelling, and pain in the proximal tissues surrounding the nail. Next the proximal and lateral nail folds separate from the nail plate, allowing discharge of the entrapped inflammatory exudate [38]. This results in a discharging horseshoe-shaped ulcer. The nail blackens and falls, exposing an unhealthy looking ulcer [33] with permanent nail deformity or anonychia. This may be the end result of untreated syphilitic paronychia. Multiple inflammatory paronychia may also occur in congenital syphilis with active manifestations [39].

Danielyan and Mokrousov [40] reported an unusual delay of 3 years before the appearance of a normal nail following adequate treatment of early secondary syphilis with penicillin. The patient was a greengrocer; there may have been minor occupational trauma that could have resulted in the Koebner phenomenon causing onychauxis.

The differential diagnosis includes acute septic paronychia, which is generally more painful, and chronic paronychia.

Tertiary syphilis very rarely affects the nail apparatus as gumata, which result in secondary necrosis with permanent nail loss when the matrix has been destroyed [41]. All individuals who have been exposed to infectious syphilis, occupationally or otherwise, within the preceding 3 months should be treated even if they show no evidence of having been infected [42].

Pinta

The nail bed may be black in patients with pinta [43].

Cutaneous diphtheria

Cutaneous diphtheria, an infectious bacterial disease, has become a rare entity following widespread immunization, but cases have been reported in travelers to endemic areas in tropical countries [44] and in a patient with AIDS [45].

Following an incubation period of 1–10 days, the lesion typically begins as a pustule that progresses to form an ulcer on exposed parts of the lower and upper limbs. The differential diagnosis includes impetigo, ecthyma, and eczema [46]. Cutaneous lesions may act as reservoirs of infection, capable of causing outbreaks of both cutaneous and the far more life-threatening pharyngeal disease. Penicillins remain the treatment of choice. Cutaneous diphtheria should be a differential diagnosis for any returning traveler presenting with a non-healing ulcer.

**Mycobacterial infections**

**Leprosy**

Leprosy is chronic infectious disease caused by *Mycobacterium leprae* and primarily affects skin and the peripheral nerves. The clinical presentation is a continuum of symptoms depending upon the host’s immunity with paucibacillary tuberculoid leprosy (TT) at one end of the spectrum (good host immunity) and highly bacillary lepromatous leprosy (LL) at the other end (poor host immunity). In between the extreme ends lie borderline tuberculoid (BT), borderline–borderline (BB), and borderline lepromatous leprosy (BL). The skin is involved as an integral part of the expression of this disease. Tuberculoid or borderline tuberculoid forms have few and symmetric skin lesions with no bacilli on skin slit smear examination or on biopsy. At the other end, skin lesions are numerous and symmetric in borderline lepromatous and lepromatous disease and acid-fast bacilli can be demonstrated on smear as well as biopsy. Leprosy (Figs 13.20–13.29; Box 13.2) can cause many nail changes, which have been observed in up to 64% of infected patients [47]. The first important reports on leprosy of nail were written by Tachikawa [48, 49].

Nail changes in leprosy are multifactorial and can be caused by neuropathy, vascular impairment, trauma, infections, and drugs used for disease management. Often more than one factor will be important. In tuberculoid leprosy neurological involvement is usually asymmetrical and appears early in the course of the disease, usually in areas of visible dermatological change. Nerve changes in lepromatous leprosy occur more slowly and are usually symmetrical, producing a “stocking and glove” anesthesia. Paradoxically, nail changes in tuberculoid and lepromatous patients are similar and occur with similar frequency, despite wide differences in pathology. The frequency of nail involvement is significantly higher

Figure 13.20 Lepromatous leprosy paronychia. Courtesy of J. Delacretaz.
in patients with disease duration of more than 5 years and in those with trophic changes secondary to the loss of sensation and impaired circulation [50].

Trophic changes are responsible for modifications of the lunula in the upper limbs; it becomes grayish and less sharply delineated from the rest of the subungual area, resulting in an apparent leukonychia manifesting as a pseudomacrolunula (Fig. 13.27). Factors only associated with lepromatous disease are invasion of the bones of the terminal phalanges by lepromatous granulomas and endarteritis occurring during type 2 lepra reactions. These may result in multiple Beau’s lines [51] and dorsal pterygium [52]. Pterygium unguis of the fingernails has also been reported as a manifestation of lepromatous leprosy [53].

The phalanges develop osteolysis and there is progressive telescoping of the digital bones [54]. When deformities such as a “preacher’s hand” occur, claw nails and other unusual appearances are produced. Dystrophic changes may occur in the nails, with progressive destruction, leaving small fragments at the corner of the nail bed, or ventral pterygium [55].

Figure 13.21 Racket nail due to acroosteolysis.

Figure 13.22 (a) Leprosy: shortening of the great toenail. (b) The same patient presenting with acroosteolysis.

Figure 13.23 Leprosy: acroosteolysis involving several fingers.

Figure 13.24 Leprosy: digit amputation. Courtesy of P. Saint-André.
Painless abscesses may occur in the periungual location with destruction of nails. This appears more often in the upper than lower limbs. Walking barefoot, the sitting position normally assumed, and the type of footwear all produce anatomical and physiological changes in the feet and legs. They may lead to pathological processes in the nails or modify those present already.

In one study of the pattern and frequency of nail changes, 300 patients with leprosy were recruited. The most common nail change was longitudinal melanonychia in the fingernails and longitudinal ridging in the toenails followed by subungual hyperkeratosis [50]. In an Egyptian study including 115 patients with leprosy and 60 patients with diabetic peripheral neuropathy, a similar incidence of nail changes was detected in both multibacillary and paucibacillary patients (86%). Nail changes were more commonly seen in patients with leprosy than in patients with diabetes (68%). The flag sign (alternating horizontal bands of whitish and pinkish discoloration of the nail) was observed in patients with leprosy [56].
Tuberculosis

Nail pathology resulting from tuberculosis (TB) is not a common occurrence, even in the TB endemic regions of the world. Painless paronychia involving a single digit of one hand may be caused by *Mycobacterium tuberculosis*, especially in paramedics handling infected specimens [57, 58]. Lesions of lupus vulgaris or tuberculosis verrucosa cutis generally occur on the trauma-prone sites on extremities, and it is not unusual for the lesions to involve nail folds, resulting in nail plate thickening, pigmentation, and Beau’s lines (Figs 13.30, 13.31). Tuberculous paronychia of the great toe with warty TB has been reported. Nail lesions may be associated with regional lymphadenitis with or without abscess formation [59]. An interesting case of tuberculous dactylitis of the great toe presenting as paronychia with pseudopterygium and nail dystrophy in an 8-year-old boy has been described (Fig. 13.32) [60]. Diagnosis is made on histology and fine needle aspiration cytology from the enlarged lymph node. Culture may be negative as cutaneous TB is generally regarded as a paucibacillary disease but DNA PCR may be done. The lesions respond to standard antituberculosis
Other mycobacterial infections

The nail fold may also be an entry point for other non-tuberculous mycobacterial infections. The most frequent example of this is *Mycobacterium marinum*, in which the point of entry may be the nail fold with the initial lesion appearing as a developing paronychia followed by granulomatous infiltration or ulceration [61]. *M. marinum* is best diagnosed by molecular methods, although it can be isolated in culture from about half the cases.

The histopathology shows a mixed infiltrate of neutrophils with lymphocytes and giant cells. Granulomas are scattered through the dermis. Treatment with cotrimoxazole or rifampicin usually with a second drug such as clarithromycin is usually effective.

Infestations

Scabies

In the ordinary forms of scabies, the clinically normal nails are not usually involved. Norwegian scabies or crusted scabies is a rare variety of scabies infestation of the skin in which the entire body, even the scalp, is affected by *Sarcoptes scabiei* (Figs 13.33, 13.34). This type of scabies consists of hyperinfestation by the scabies mite with the mites numbering in the millions. The lesions of Norwegian scabies are strikingly different in clinical appearance than ordinary scabies. Patients have generalized hyperkeratotic crusted and psoriasis-like

Figure 13.31 Tuberculosis verrucosa cutis around the toenail.

Figure 13.32 Tuberculous dactylitis presenting with paronychia and pseudopterygium. Courtesy of D. Khanna.

Figure 13.33 Norwegian scabies in Down syndrome. Courtesy of J. Beurey.

Figure 13.34 Norwegian scabies: isolated subungual hyperkeratosis. Courtesy of R. de Paoli and V. Marks.
scaly lesions along with subungual accumulations of scales on the fingers and toes [62]. It is an extremely contagious form of scabies, most often seen in the elderly, those with a low intelligence quotient, and immunosuppressed patients as well as patients with HIV and AIDS (Box 13.3).

As the pruritus is mild or absent in this form, scabies is often misdiagnosed, leading to large nosocomial outbreaks. Chronic eczematoid dermatosis, atopic eczema, lichen simplex, and psoriasis may be mimicked by this condition [63], and topical use of corticosteroids may alter the clinical appearance of scabies.

One of the characteristic manifestations of crusted scabies is the existence of a thickened, dystrophic, and discolored nail plate affecting several fingernails and/or toenails with hyperkeratotic debris beneath. The subungual debris harbors large numbers of mites. On scratching, the mites get caught under the nail, where they colonize in the subungual and periungual region. From there they extend proximally [64] and may be inoculated into all parts of the body during scratching. Even after seemingly successful treatment of skin lesions, the mites survive in these dystrophic nails and may be responsible for the persistence of infestation. The distal subungual area may provide a nidus for mites, a source for small epidemics in hospitals and nursing homes [65]. In a single case report in an immune-competent man, an initial lesion of subungual scabies led to recurrent skin lesions of ordinary scabies and a small outbreak of scabies in nurses. The patient was discovered to have thickened and whitened toenails with subungual horny debris containing innumerable mites and eggs [66]. Crusted scabies of long duration has also been reported to cause longitudinal splits in the majority of the finger and toenails that extended almost along their entire length of the nail plate [67].

Potassium hydroxide examination of subungual debris under a microscope shows abundant mites, eggs, and fecal pallets. Histopathology shows that the hyponychium may be infested with *Sarcoptes hominis* (*Acarus scabiei*) in elderly people. Tangential biopsies of the hyponychial keratosis with the overlying free edge of the nail plate may show mite burrows containing mites, eggs, and feces. In Norwegian scabies, the nail may be elevated by marked subungual hyperkeratosis with alternating parakeratosis and orthokeratosis. Abundant mites are usually present. A heavy mixed infiltrate often containing many eosinophils is seen in the dermis.

The subungual material with abundant mites may not respond to topical therapy alone. Frequent trimming of nails and treatment twice daily with permethrin is recommended. In resistant cases this should be supplemented by surgical scrubs using a scabicide and/or by 40% urea nail dissolution and partial nail avulsion [68]. Oral ivermectin has been used with great success in crusted (Norwegian) scabies, although its effects on nail involvement have not been well documented [69]. Daily occlusive dressing of the toenails with 5% salicylic acid and 1% lindane in petrolatum for 2–4 weeks has been reported to be an effective therapy for subungual scabies [62, 65].

**Pediculosis**

Interestingly, pediculosis of the foot, limited to the hallux, has also been reported [70] in a patient with onychomycosis of all toenails, which were thickened. Debridement of the right great toenail exposed multiple cavities, housing approximately 10–12 body lice.

**Tungiasis**

Tungiasis (Figs 13.35, 13.36) is an infestation caused by the fertilized female sand flea *Tunga penetrans* and has

---

**Box 13.3  Risk factors for developing crusted scabies**

- Advanced age
- Severe malnutrition
- Vitamin A deficiency
- Dementia/low intelligence quotient
- Down syndrome
- Leprosy
- Tabes dorsalis and syringomyelia
- AIDS and HIV
- Malignancy
- Radiotherapy
- Iatrogenic Cushing syndrome
- Prolonged use of immunosuppressive drugs
- Human T-cell lymphotropic virus 1 infection
- Adult T-cell leukemia/lymphoma
- Systemic lupus erythematosus
- Institutional accommodation – psychiatric hospitals/prisons and assisted living communities

---

Figure 13.35 Tungiasis. Courtesy of R. Pradinaud.
been noted primarily in patients who have recently traveled to endemic areas such as Central and South America, the Caribbean, sub-Saharan Africa, the west coast of India, and Pakistan.

The flea burrows into the epidermis. Clinical features of tungiasis consist initially of a pruritic, tender or painful, small erythematous papule with a central black dot produced by the posterior part of the flea’s abdominal segments. The fully developed lesion is a white pea-sized nodule with a central black or brown pit or plug located in the subungual and periungual areas of the toes or the soles. Complications include cellulitis, gangrene, auto-amputation of toes, and tetanus [71].

The clinical differential diagnosis of tungiasis includes fire ant bite, tick sting, scabies, creeping eruption (*Ancylostoma* spp), cercarial dermatitis, and myiasis.

Definitive diagnosis rests upon demonstration of the flea using a mineral oil preparation or by examination of a biopsy specimen. This reveals an intraepidermal cystic cavity lined by an eosinophilic cuticle. The cavity contains ring-shaped portions of the organism’s respiratory and digestive tracts as well as multiple round to oval eggs that may contain a pale-staining round yolk sac [72, 73].

Treatment varies from physically removing the flea with a sterile needle to application of 4% formaldehyde solution, DDT, chloroform, paraffin, or turpentine. Systemic niridazole has been recommended if there are multiple sites of infection. Topical and sometimes systemic antibiotic treatment are advised in addition to tetanus immunization. Wearing of shoes is the primary defense against tungiasis [74].

**Subungual myiasis**

Infestation by larvae of *Musca domestica* is unusual in a subungual location (Fig. 13.37). Nevertheless, 3 days after a traumatic event, Muñyon and Urbanc [75] noted a subungual hematoma of the great toenail in a white female. The portion of the hematoma underneath the proximal nail fold was found to be teeming with larval forms.

Other cases have been reported with larvae identified as *Sarcophaga* spp [76, 77]. Faulde et al. [78] described the first case of subungual human *Limothrips cerealium* infestation associated with onychomycosis and subungual myiasis. *Calliphora* spp larvae were found in a woman with mental illness [79]. A case of periungual myiasis by *Wohlfahrtia magnifica* in a 5-year-old girl with good hygiene has been reported following her holidays in Kenya. Clinically, the child presented with inflammation of the right great toe masquerading as an ingrowing toenail [80].

In general, myiasis should be considered in patients with insufficient personal hygiene, especially those with chronic mental illness.
**Trichinosis**

The etiological agent *Trichinella spiralis* settles in the nail bed vasculature through hematogenous spread, resulting in splinter hemorrhages that are known to occur simultaneously in all nails and begin proximally [81, 82]. Histopathology may reveal the organism. Other cutaneous signs of the disease such as solid facial edema or periorbital edema are usually present with or without systemic symptoms. Diagnosis is by fluorescent antibody testing by enzyme-linked immunosorbent assay.

**Parasitic infections**

**Leishmaniasis**

Cutaneous leishmaniasis, endemic in the Middle East, North Africa, Asia, and Central and South America, is caused by an intracellular protozoan parasite of genus *Leishmania* and transmitted by female phlebotomine sandflies. Lesions of cutaneous leishmaniasis with a central ulcerated crater and elevated edge may involve the dorsum of the distal phalanx (Fig. 13.38).

Cutaneous leishmaniasis may present as chronic paronychia-like lesions with ulcerative, infiltrative, and verrucous lesions involving the proximal and lateral nail folds of the fingers and uncommonly toes [83–85]. In one case, coexistent whitlow and paronychial lesions have been reported [86]. A high index of suspicion is necessary for paronychia refractory to standard antibiotics and antifungal therapy. A history of a recent visit to an endemic region may aid the diagnosis. Diagnosis is confirmed by demonstration of the amastigote form of the leishmanial parasite, *Leishman* trophozoite bodies both within and outside the macrophages, on slit skin smear examination, or in histopathology samples. Treatment options include topical paromomycin, intramuscular or intravenous sodium stibogluconate, oral itraconazole, intravenous amphotericin B, or oral miltefosine.

In post-kala-azar dermal leishmaniasis, verrucous lesions may be seen in the vicinity of the nail unit and chronic paronychia-like lesions have also been described.

**Cutaneous larva migrans**

The most common etiological agent is hookworm larvae of *Ankylostoma braziliense*, acquired by walking barefoot on sandy beaches contaminated with animal feces. Intense pruritic migratory serpiginous burrows on the dorsum of the terminal phalanx have been reported with secondary dystrophic nail changes, possibly due to infection of the nail matrix (Fig. 13.39) [87]. Oral albendazole or ivermectin is effective.
Malaria

Changes in nail color occur during acute episodes. Immediately prior to the fever, the nails become pale gray and this is maintained throughout the pyrexia. Nail bed pallor has been shown to be 85% sensitive and 41% specific in identifying parasitemic children [88]. Subungal hemorrhages, striate leukonychia, and koilonychias are described in quartan malaria, as are multiple transverse, dark brown lines and furrows. Beau's lines may occur following infection with *Plasmodium vivax* malaria [89].

References

Bacterial, Viral, and Other Infections

34 Adamson HG, McDonagh JER. (1911). Two unusual forms of syphilitic nails: with some general remarks upon syphilis of the nails. Br J Dermatol. 23: 68.
NON-PSORIATIC DISORDERS

Bianca Maria Piraccini and Mark Holzberg

Pityriasis rubra pilaris

Nail involvement is common in adult acute-onset type I pityriasis rubra pilaris (PRP), especially if the palms and soles are involved [1]. Familial cases occur and the pattern of inheritance is usually autosomal dominant. Finger nails reveal subungual hyperkeratosis with moderate thickening of the nail bed, splinter hemorrhages, longitudinal ridging (onychorrhexis), and a distal yellow-brown discoloration (Figs 14.1, 14.2). Histologically, matrix involvement creates patchy parakeratosis in the nail plate.

Nail dystrophy is less common in the juvenile forms of PRP. In a case report of a young girl with an atypical case of juvenile type V PRP, Lambert and Dalac [2] described onychogryphosis of all 20 nails (Fig. 14.3). A 6-year-old boy was reported with associated hypoparathyroidism and brachyonychia [3]. Paronychia and redness of the lunula may be observed when palmar involvement is severe.
Psoriasiform pitting may occur in the absence of any periungual abnormality in localized, circumscribed juvenile type IV PRP. Histologically the nail bed epithelium reveals parakeratotic areas, acanthosis, and focal basal liquefaction [4]. Keratohyalin may be seen. In the dermis,

Figure 14.1 (a,b) Type I pityriasis rubra pilaris: prominent distal subungual thickening. Courtesy of A. Griffiths.

Figure 14.2 Type I pityriasis rubra pilaris: mild subungual hyperkeratosis, splinter hemorrhages, and distal yellow-brown discoloration.

Figure 14.3 Type V pityriasis rubra pilaris: onychogryphosis. Courtesy of D. Lambert.

(Fig. 14.4). Psoriasiform pitting may occur in the absence of any periungual abnormality in localized, circumscribed juvenile type IV PRP. Histologically the nail bed epithelium reveals parakeratotic areas, acanthosis, and focal basal liquefaction [4]. Keratohyalin may be seen. In the dermis,

Figure 14.4 Juvenile pityriasis rubra pilaris: paronychia and redness of the lunulae.
Dermatological Disorders

there is a mononuclear inflammatory infiltrate. The hyponychium shows both orthokeratosis and parakeratosis.

In AIDS, nail changes have been reported in PRP-like disease [5]. Wedge-shaped thickening without subungual hyperkeratosis has been described in a patient with type VI PRP associated with HIV [6]. Possible treatments include etretinate [7], combined oral retinoid–photochemotherapy (PUVA) treatment, and tumor necrosis factor (TNF)-α antagonists (infliximab, etanercept, and adalimumab) as monotherapy or in combination with methotrexate and acitretin [8, 9].

Pityriasis rosea

Silvers and Glickman [10] reported a 32-year-old patient who developed onychodystrophy 2 months after a bout of pityriasis rosea. The nail changes were characterized by multiple transverse indentations and pitting in the nail plate. Rectangular areas of dystrophy were observed in the middle third of each nail.

Pityriasis lichenoides acuta

Permanent nail dystrophy has been associated with acute “vasculitic” and necrotic pityriasis lichenoides acuta in one case (Fig. 14.5).

Parakeratosis pustulosa

See Chapter 10.

Lichen planus

Nail involvement occurs in 2–20% of patients with skin or oral lichen planus and may also be associated with lichen planopilaris and frontal fibrosing alopecia [11]. Lichen planus of the nail without skin involvement can also occur, making the diagnosis more difficult. In two studies on cases of histopathology-proven nail lichen planus, only 25% of patients with nail lichen planus had lichen planus in other sites before or after the onset of nail lesions [12, 13].

Heredit plays a role in lichen planus, but there are no reports about occurrence of nail lichen planus as an inherited trait. In addition to heredity, primary immunological disturbances are thought to represent another factor in the pathogenesis of the disease. Nail lichen planus may be associated with autoimmune disorders or with disorders characterized by altered immune response, including alopecia areata, vitiligo, autoimmune thyroid disease, celiac disease, chronic inflammatory liver diseases, psoriasis, atopic dermatitis, localized scleroderma, polymyalgia, and Sjogren syndrome [14].

Stress was an evident triggering factor in 20% of patients in a study of 20 cases [13].

Prevalence of nail lichen planus is equal in males and females, although a large study reported a higher prevalence in males [15]. The ages most affected are the fourth or fifth decade of life although, even if rarely, children may be affected (see Chapter 10).

Clinical features

Usually several or most nails are affected, with the thumbs showing the most severe changes.

The clinical features depend upon the site affected by the pathological process.

Nail fold lichen planus

Typical violaceous papules of cutaneous lichen planus can occur on the proximal and lateral nail folds (Fig. 14.6). The proximal nail fold may also show a diffuse bluish-red discoloration with or without swelling, with evident Wickham striae (Fig. 14.7).

Nail matrix lichen planus

Longitudinal ridging (onychorrhaxis) is the most common sign of lichen planus in the nail [12–14]. The nails show longitudinal ridges and grooves, thinning,

Figure 14.5 (a–c) Pityriasis lichenoides acuta. Courtesy of R. Russell-Jones.
and distal fissuring and splitting (Fig. 14.8). Severe thinning and distal splitting leads to considerable nail shortening (Fig. 14.9). These changes are due to inflammatory foci in the nail matrix. The inflammation may be spotty across the matrix and thus results in a nail plate that is differentially thinned and ridged (Fig. 14.10). In the same way, the inflammation may differ from nail to nail (Figs 14.11, 14.12). Nail signs are best seen in the fingernails, as typical signs of matrix lichen planus are uncommon in the toenails (Figs 14.13, 14.14).

Punctate or diffuse redness can appear in the lunula [16] and may be seen in approximately 25% of cases of lichen
planus of the nails [12] (Figs 14.15, 14.16). It is a sign of inflammation of the distal nail matrix. A longitudinal red streak may be observed in the nail plate (longitudinal erythronychia) (Fig. 14.10). A transitory longitudinal melanonychia may result from activation of nail matrix melanocytes [17]. It has been reported as an isolated finding (Figs 14.17–14.19) [17, 18] and after treatment using intramuscular injections of triamcinolone acetonide [19]. In African Americans, postinflammatory hyperpigmentation may involve several nails and the nail bed (Fig. 14.20).
Figure 14.15  Mottled lunulae in nail matrix lichen planus.

Figure 14.16  Diffuse red discoloration of the lunulae in nail matrix lichen planus.

Figure 14.17  (a) Longitudinal melanonychia in lichen planus. (b) Histology of the matrix area in the same patient.

Figure 14.18  Longitudinal melanonychia associated with nail matrix lichen planus.
Complete and severe matrix involvement may result in marked thinning and shortening of the nail plate until complete loss of the plate with nail bed scaling occurs (Figs 14.21–14.24).

The development of dorsal pterygium is virtually pathognomonic for lichen planus. Dorsal pterygium is a sign of nail matrix destruction, due to inflammation involving both the matrix and the overlying proximal nail fold. These two structures fuse and scar, resulting in a V-shaped extension of the proximal nail fold to the nail bed. If the scar involves the medial part of the matrix, the nail plate splits into two parts (Fig. 14.25). The term pterygium derives from the Greek word for wing and describes the appearance of the nail where two wings are divided by a spine of scar tissue. Observation of the nail by dermoscopy shows that the skin of the proximal nail fold continues distally (Fig. 14.26). If the scar is lateral, the result is a narrow nail plate (Fig. 14.27). Several pterygia may be present in the same nail (Fig. 14.28). Development of pterygium is not related to duration of the disease [12], and usually only one or two nails are affected (Figs 14.29, 14.30). Progressive widening of the pterygium occurs with progressive scarring of the matrix.
Figure 14.23 Severe nail matrix lichen planus with total or partial absence of the nail plate associated with skin lichen planus.

Figure 14.24 Severe nail matrix lichen planus with massive nail plate thinning and shortening, better seen at dermoscopy.

Figure 14.25 Dorsal pterygium: the skin of the proximal nail fold extends distally to the nail bed in a V-shaped structure.

Figure 14.26 Dorsal pterygium: dermoscopy shows how the skin of the proximal nail fold extends distally to the nail bed in a V-shaped structure (arrow).
Even lichen planus subsides with treatment; pterygium will prevent normal nail regrowth, as it is a permanent scar.

A rare form of nail lichen planus results from transient spotty proximal nail matrix inflammation with formation of pitting. Numerous pits may appear ridged.

**Figure 14.27** (a) Dorsal pterygium of the fifth fingernail, resulting in a narrow nail plate that is easily seen by onychoscopy (b).

**Figure 14.28** Several narrow pterygia in the same nail.

**Figure 14.29** Dorsal pterygium due to nail lichen planus involving two fingernails.

**Figure 14.30** Dorsal pterygium due to nail lichen planus involving the toenails.

**Figure 14.31** Nail matrix lichen planus producing numerous pits and longitudinal fissures resulting in rough nails (trachyonychia).

Even lichen planus subsides with treatment; pterygium will prevent normal nail regrowth, as it is a permanent scar.

A rare form of nail lichen planus results from transient spotty proximal nail matrix inflammation with formation of pitting. Numerous pits may appear ridged.
(onychorrhexis) or rough (trachyonychia) (Fig. 14.31) and the free edge may be ragged and split.

Trachyonychia due to nail matrix lichen planus is an uncommon finding, and is mainly seen in children [20–22]. It can involve one (Figs 14.32, 14.33) or several nails. Diagnosis of trachyonychia due to lichen planus requires a biopsy, even if this is not required in trachyonychia.

In the toenails, both classic and bullous nail matrix lichen planus often cause longitudinal fissures and distal splitting together with nail plate thickening [23, 24]. The nails may acquire a yellow discolouration (Fig. 14.34) that mimics the yellow nail syndrome, but fingernails show typical features of matrix lichen planus (Fig. 14.35).

**Nail bed lichen planus**

Nail bed lichen planus produces onycholysis and more or less severe subungual hyperkeratosis alone (Figs 14.36, 14.37) or in combination (Fig. 14.38). Onycholysis may start proximally. If the onycholysis is complete, shedding of the nail plate (onychomadesis) can occur. Permanent atrophy may result.

A characteristic finding in nail bed lichen planus is the “pup tent” sign, in which the nail plate splits, elevates longitudinally, and the lateral edges angle downward (Fig. 14.39) [25]. Isolated lichen planus of nail bed is rare, as nail bed involvement is usually seen in conjunction with matrix disease (Figs 14.40, 14.41).

A massive, hard, nail bed hyperkeratosis characterizes the hypertrophic variant of nail lichen planus. The nails are thickened, whitish, and difficult to trim (Fig. 14.42). A case of massive nail thickening associated with paronychia, severe palmoplantar keratoderma, and diffuse skin lichen planus in a 52-year-old man was reported by Sehgal et al. [26].

**Variants**

Uncommonly, lichen planus can present as a keratotic tumor of the nail bed in a single finger [27] (Fig. 14.43).

Ulcerative/bullous lichen planus is a rare variant, when nail lesions combine with bullae and erosions on the soles and occasionally on the palms [28–33]. The great toes are the most commonly affected but involvement of the fingernails can also occur. The nail bed shows a large erosion associated with marked inflammation and possible erosions of the surrounding tissues (Figs 14.44, 14.45). This painful condition leads to permanent anonychia (Fig. 14.46). Ulcerative lichen planus may present as permanent anonychia as the only manifestation of the disease (Fig. 14.47) [34]. Nail degloving is another possible sequela [35]. In a patient with involvement of 10 fingernails, Baran and Perrin [35] observed a whitish material at the base of the nail plates and a swollen proximal nail fold. When progressive pressure was applied, the whitish material became more prominent and an
advancing extrusion of the entire nail apparatus rigid enough to mimic a balloon fish that was completely open at the rear was observed. The pathology showed a hyperkeratotic and pseudobullous nail lichen planus with dramatic evidence of avulsed epithelial structures (ventral portion of the proximal nail fold, matrix, nail bed, and hyponychium) seemingly ejected from their dermal base [35].

“Idiopathic atrophy of the nails” is considered to be a rare and extremely severe variety of nail lichen planus, and is seen especially in African and Asian patients [36–40]. It presents clinically as a rapid progressive atrophy of the nail and loss of the nail plate with or without pterygium (Figs 14.48, 14.49). It is asymptomatic and there is often an absence of other cutaneous signs. Most of the digits are affected.

Patients with scalp lichen planopilaris may present with acquired leukonychia of all 20 nails (Fig. 14.50) [41, 42]. The pathogenesis is thought to be due to a focus of inflammation in the ventral proximal nail fold.
Chapter 14

Figure 14.37 Lichen planus of the nail bed presenting with onycholysis that starts proximally.

Figure 14.38 Lichen planus of the nail bed: onycholysis and subungual hyperkeratosis.

Figure 14.39 “Pup tent” sign of nail lichen planus in the thumb: the split nail plate is uplifted centrally with the lateral parts going downward.

Figure 14.40 Lichen planus of the nail bed and nail matrix: onycholysis is associated with nail thinning, longitudinal fissuring, and distal splitting.

Figure 14.41 Lichen planus of the nail bed and nail matrix: onycholysis is the prevalent feature in the first and fifth fingernails, while nail thinning and longitudinal fissuring prevail in the second, third, and fourth. Note dorsal pterygium in the third fingernail.
Dermatological Disorders

report of 45 patients with lichen planopilaris of the scalp, Mehregan et al. [43] found that 25% of patients had nail involvement at presentation of their scalp disease and one developed nail disease subsequently. Interestingly, there are many similarities between nail lichen planus and lichen planopilaris of the scalp. Both may occur without any cutaneous or mucous membrane disease, both can cause permanent destruction and scarring of the underlying anatomical site, and the histology is similar.

**Differential diagnosis**

When nail changes occur in a patient with lichen planus of the skin, the diagnosis of lichen planus of the nail is relatively easy. However, when only disease limited to the nails is the presenting sign, accurate diagnosis may be difficult. To complicate this, lichen planus has the potential to cause permanent scarring and so early diagnosis is crucial. Often a biopsy, especially early in the course of the disease, is important so that early treatment can be instituted.

The differential diagnosis of lichen planus in the nail includes other diseases that induce nail thinning with longitudinal ridging, i.e. nail aging and radiodermatitis. Skin diseases such as psoriasis and lichen striatus may resemble the clinical changes seen in nail lichen planus. Nail pterygium may result from causes other than lichen planus, including Stevens–Johnson syndrome, severe bacterial infection, or trauma to the matrix and peripheral
vascular disorders. Changes in toenail lichen planus may mimic yellow nail syndrome [24, 25]. Systemic amyloidosis may produce uniformly thinned, brittle, longitudinally ridged (onychorrhexis) nails that are split distally [44]. Biopsy-proven lichen planus taken from characteristic thin, rough nails and from the skin arose as an allergic reaction to mercury in a 61-year-old man with mercury-laden dental alloy [45]. Suspicion should arise if lichen planus is present in one nail and is of long duration.

In a series of patients with oral or nail lichen planus who were patch tested for metal allergy, six of the 10 patients with nail lichen planus and a metal allergy improved after removal of dental materials containing the causative metals or with systemic disodium cromoglycate therapy [46].

Longitudinal striation, distal splitting, and nail plate atrophy typical of lichen planus were seen in three cases of in situ amelanotic melanoma [47].
Histopathology

Lichen planus in the nail shares many histological features with its counterpart in lichen planus of the skin. Histologically, lichen planus is characterized by a sawtooth appearance of the epithelial rete ridges, compact orthokeratosis, wedge-shaped hypergranulosis, irregular acanthosis, damage to the basal cell layer, a band-like inflammatory infiltrate in the upper dermis, and, commonly, marked spongiosis of the matrix and nail bed epidermis. The infiltrate may exhibit epidermotropism. Lymphocytes predominate in the infiltrate with a few macrophages, eosinophils, and plasma cells. An infiltrate primarily of plasma cells has been described [48]. Melanophages are often found in the upper dermis adjacent to the damaged basal cells. Observations from one series of 24 patients with nail lichen planus allow generalizations concerning histological features at the different sites in the nail unit [12]. Longitudinal ridges, depressions, and superficial fragility (Fig. 14.51) are usually due to involvement of the eponychium, proximal tip, and proximal part of the matrix. Foci of matrix hypergranulosis produce irregular keratin, which leads to nail plate irregularities such as ridges or atrophy. Hypergranulosis in the nail bed produces keratin that does not adhere to the nail plate keratin, giving rise to subungual hyperkeratosis and/or onycholysis. Unusually severe liquefactive degeneration of the basal layer of the nail bed has been shown to cause isolated bullous lichen planus of the nails [30]. Longitudinal melanonychia rarely occurs in lichen planus and is probably due to activation of melanocytes by the inflammatory process and melanocyte destruction [17].

Treatment

Treatment for lichen planus of the nails is often directed against the extent of the inflammatory response present. Mild forms of lichen planus may resolve spontaneously, and so, often, no treatment is necessary. If the cutaneous surface is involved, treating it may also improve nail changes. However, more severe inflammation and potentially scarring disease should be treated more aggressively to prevent permanent dystrophy.

Corticosteroids are the mainstay of therapy. Potent fluorinated corticosteroids can be used topically under occlusion. Intrallesional triamcinolone can be used when individual digits require treatment [49]. Dilute intrallesional triamcinolone in doses of 3–5 mg/mL can be used monthly. Injection sites should be at the lateral distal digit at the sites of the matrix and nail bed so that the solution can diffuse to the center of the digit to bathe the undersurface of these structures.

Oral or intramuscular corticosteroids are very helpful and may be needed to halt destruction. Treatment with intramuscular triamcinolone acetonide 0.5 mg/kg per month in adults led to resolution of onychodystrophy after 2–6 months of treatment (Figs 14.52, 14.53) [12]. The toenails may take more time to improve, and some longitudinal fissures may remain (Fig. 14.54). As much as
60 mg per day of prednisone may be needed. In one series, 0.5 mg/kg was given on alternate days for an average of 3–6 months, resulting in total resolution of the nail changes [12]. About two-thirds of patients respond to systemic steroid treatment, independently of age and severity of disease [14].

In addition to topical corticosteroids, other topical medications have been used in nail lichen planus. Topical tacrolimus has been used with success in five cases [50]. Systemic treatments that have been reported effective in single patients include: fumaric acid esters, which were helpful, at lower dosage than recommended for psoriasis, in a 37-year-old patient with lichen planus of the fingernails over a 7-month period [51]; oral etretinate, used successfully at a dose of 0.4 mg/kg in combination with topical fluocinonide lotion in a 46-year-old Japanese patient [52]; oral azathioprine, which has been reported as successful therapy in two adults with erosive lichen planus with nail involvement [53]; ciclosporin, successfully utilized in a patient with palmoplantar and nail lichen planus of the palms [54]; and etanercept, which led to a marked improvement of relapsing toenail lichen planus in a 53-year-old woman [55]. Alitretinoin seems a promising agent for nail lichen planus resistant to other therapies at a dosage of 30 mg daily, which has been effective over a period of 6–9 months in several published reports [56–58].

**Prognosis**

A poor prognosis was reported in two rare and severe variants of nail lichen planus, i.e. idiopathic atrophy of the nails, which is often diagnosed when the matrix has already been widely destroyed and therapy may only stop progression of scarring within the nail, and the bullous variant of nail lichen planus, in which scarring and total nail loss are the outcome of treatment.

The prognosis of the classic forms of nail lichen planus is dependent upon the degree of matrix involvement, resultant scarring, and pterygium formation. The development of severe and early destruction of the nail matrix characterizes a small subset of patients with nail lichen planus [12]. In these patients, when the inflammatory response is marked, the destructive process can be halted.
early and irreversible damage may be avoided. If the matrix and nail bed are completely involved with an exu­berant destructive inflammatory process, a total loss of the nail plate and permanent atrophy with scarring will result. In a long-term follow-up of 27 patients with biopsy-proven lichen planus treated over more than 5 years (mean 10 years), 18 (66.7%) were cured, 11 (40.7%) relapsed, and nine (33.3%) did not respond to intramuscular or intralesional corticosteroids [14].

The 20-nail variant or trachyonychia does not produce nail scarring and often resolves spontaneously.

A case of squamous cell carcinoma has been reported as a complication of a 10-year course of nail lichen planus treated with topical steroids [59].

**Lichen nitidus**

See Chapter 10.

**Lichen aureus**

Lichen aureus is an uncommon subtype of chronic pig­mented purpuric dermatosis that most often affect the lower extremities of young adults and presents clinically as well-circumscribed golden brown confluent macules and papules. Its association with nail changes is rare (Fig. 14.55) and has been reported in a 45-year-old man who presented with symmetric copper-colored papules in a linear pattern affecting the proximal nail folds of the hands and feet. Histology showed lichen aureus [60].

---

Figure 14.53 Nail lichen planus successfully treated by intramuscular triamcinolone acetonide for 6 months.

Figure 14.54 Nail lichen planus of the toenails successfully treated by intramuscular triamcinolone acetonide for 6 months. Some longitudinal ridges persist.
Keratosis lichenoides chronica

Keratosis lichenoides chronica is a rare disorder consisting of the progressive development of asymptomatic lichenoid and verrucous lesions on the limbs and the trunk in a somewhat linear distribution, which may be associated with a seborrheic dermatitis-like eruption on the scalp and face [61]. Extension to the palmoplantar skin is commonly seen with involvement of the nails in approximately one-third of cases [62, 63]. Changes in the nail may be seen in the periungual skin, the nail plate, and the nail bed [64, 65]. The nail fold may exhibit a paronychia with or without a linear or warty hyperkeratotic hypertrophy of the periungual tissues (Fig. 14.56).

Transverse overcurvature, thickening, yellow-brown discoloration, longitudinal ridging, and fragmentation of the free margin may be observed in the nail plate. Subungual hyperkeratosis, onycholysis, and splinter hemorrhages may be seen in the nail bed [66].

Eczema

Eczema refers to a broad category of dermatitis characterized histologically by inflammation and spongiosis of the epidermis. These include atopic dermatitis, nummular dermatitis, allergic contact dermatitis, irritant contact dermatitis, and more. The diagnosis will come from a good history and physical examination of the configuration and distribution of the rash on the cutaneous surface. Patch tests can be used to rule out a contact allergy.

The inflammatory infiltrate may involve the proximal nail fold, with or without the nail matrix, the nail bed, and the hyponychium, resulting in a variety of different signs and symptoms (Fig. 14.57). In a study of 777 consecutive patients with atopic eczema by Simpson et al. [67], hand involvement was observed in 58.9% and nail dystrophy was seen in 16%. Another study reported a prevalence of nail plate changes in 90.7% of 140 patients with hand eczema [68].

When eczema occurs on the proximal and lateral nail folds, erythema, edema, and loss of the cuticle can result. They can be associated with typical eczema of the dorsum of the fingers (Figs 14.58, 14.59). Periungual pyogenic granuloma arising from the inflamed proximal nail fold is a rare occurrence (Fig. 14.60) [69]. Subacute or more chronic disease may result in background erythema, mild swelling, and loss of cuticle characteristic of a chronic paronychia.

Eczema of the proximal nail fold is very likely to affect the most proximal part of the matrix, resulting...
in alterations in the nail plate surface (Fig. 14.57). The nail plate may appear thickened, discolored, and rough. Pitting may be present. If the inflammation is recurrent and intermittent, a Beau’s line may appear in the nail plate. Onychomadesis may occur.

Eczematous changes in the nail bed and hyponychium are often a sign of allergic contact dermatitis. The most common causes are toluene sulfonamide formaldehyde resin contained in nail lacquers, and various types of acrylates contained in sculptured/artificial nails and preformed plastic tips [70–74]. Periungual eczema and pitting may also be seen in occupational allergic contact dermatitis to (meth)acrylates among nail technicians, dentists, printers, and fiberglass workers. Other possible causes of contact allergy are topical substances or drugs applied on the nail plate and periungual tissues [75–78]. Nail changes resulting from allergic contact sensitivity of the nail bed/hyponychium may appear hours to even weeks after contact with the allergen. It may also appear at distant sites, including the face and neck [73]. Early changes are splinter hemorrhages, which soon may be followed by the development of onycholysis and subungual hyperkeratosis and/or paronychia (Figs 14.61, 14.62). Erythema, scaling, and fissuring may result (Figs 14.63, 14.64). The affected areas may be fairly painful.

Irritant contact dermatitis of the nail bed causes similar changes.

In atopic dermatitis, constant rubbing and scratching of the skin causes the nails to be buffed; the surface of the nails becomes polished and shiny.

Figure 14.57 (a–e) Eczema – spectrum of the nail changes that may be seen.

Nail care and careful cleaning are important in atopic individuals, as the subungual space is an important reservoir of *Staphylococcus aureus*. The prevalence of *Staphylococcus* beneath the nails in atopics is 10-fold greater than in normal controls [79], and scratching may contribute to its spreading over the skin.

Treatment of the nail folds with topical corticosteroids is often helpful in patients with atopic eczema. An antibiotic may be needed for secondary bacterial infection. Corticosteroid use must always be balanced.
Figure 14.59 Acute allergic contact dermatitis of the hands and fingernails due to vinyl gloves.

Figure 14.60 Acute eczema of the proximal nail fold with paronychia and a pyogenic granuloma of the proximal nail fold of the thumb in atopic dermatitis.

Figure 14.61 Paronychia, onycholysis, and subungal hyperkeratosis in allergic contact dermatitis to topical preparations.

Figure 14.62 Paronychia, onycholysis, and subungal hyperkeratosis in allergic contact dermatitis to acrylates.
against the increased risk of secondary infection such as osteomyelitis of the distal phalanges as reported in three children [80]. Topical tacrolimus under occlusion has been used with some success in a patient reported by Lee et al. [81].

**Discoid lupus erythematosus**

Discoid lupus erythematosus is a chronic autoimmune disease of the skin characterized by inflammatory plaques and scarring most commonly on the face, ears, and scalp. It can involve the limbs and, very uncommonly, the nail folds and nails. Nail changes alone have never been reported to occur [82]. Even though the nail changes in discoid lupus are not pathognomonic, the diagnosis may be suspected when the presenting signs are paronychia with erythema, atrophy, and scaling, which may be associated with a typical red-blue diffuse discoloration of the nail bed, onycholysis and scaling, and crusted subungual hyperkeratosis and dystrophic nail plates that tend to crumble (Figs 14.65, 14.66) [83].

The periungual skin may vary from normal to reddish with brownish-grey adherent scales [83]. The changes in the nail fold may be identical to what is seen in discoid lupus in the skin [82].

Nail matrix inflammation leads to changes in the nail plate (onychorrhhexis). Distally, the nail plates crumble and become fragile, irregular, and split. Finger clubbing has been reported in one patient with lupus erythematosus [84]. In hypertrophic lupus erythematosus, palmo-plantar hyperkeratosis may extend onto the dorsa of toes to surround the nails; longitudinal ridging (onychorrhhexis) and subungual hyperkeratosis are observed [82, 85]. When nail matrix and nail fold inflammation is severe, scarring and pterygium may result.
In the nail bed, the red-bluish discoloration may be diffuse or punctate. Scarring and sclerosis may occur [86].

Lupus erythematosus unguium mutilans is a variant of discoid lupus in which the nail has a cyanotic tinge and adherent scales [87]. Subungual friable yellowish-brown material may lift up the nail plate; the nail may be totally destroyed, leaving the nail bed exposed as a deep red, shiny area [88]. Horny growths on the fingers may be accompanied by opaque, thickened nail plates with a dirty grayish discoloration and shallow longitudinal furrows [89].

In another variant, chilblain lupus erythematosus, which occurs sporadically in the acral regions in middle-aged women including the periungual tissues, clinical examination reveals red-to-violaceous infiltrated and slightly scaling plaques that typically worsen during the cold season [90, 91]. A gross distortion of the nail plates may be associated [92].

Discoid lupus erythematosus and lichen planus have much in common in the nails both clinically and histologically. Scarring is a major component of each. However, nail involvement in discoid lupus is less common than in lichen planus, and the focus of scarring is more in the nail fold than in the matrix. Nevertheless, in aggressive discoid lupus of the digit, nail destruction with pterygium formation may occur as in lichen planus.

Histologically, lupus erythematosus of the periungual skin shows characteristic hyperkeratosis, liquefaction degeneration of basal cells, a predominantly lymphocytic infiltrate in the superficial dermis, and edema with ectatic capillaries in the papillary dermis [84]. In the nail bed, hyperorthokeratosis with a corresponding granular layer, thinning of the spinous layer, and edema of the basal cells are observed. Hyaline bodies are observed in the superficial dermis [83].

Potent topical steroids have been used in discoid lupus and may lead to some improvement.

**Bullous pemphigoid**

Bullous pemphigoid is an autoimmune subepidermal blistering disease that more commonly occurs in the elderly. The anatomic location of the epithelial detachment is what determines the clinical change in the nail. Most commonly, the nail fold is involved, with paronychia and bullous lesions of the skin of the dorsum of the digits as clinical signs (Fig. 14.67), but matrix and nail bed blistering also occurs, with onychomadesis and onycholysis with bed erosion (Fig. 14.68) [93–95]. The inflammatory disease may be so severe as to produce scarring and pterygium. Isolated localization to the toenail has been reported [96]. Barth et al. [97] reported longitudinal splitting in the nail plate.

Childhood disease is uncommon. In a case report of a 4-year-old girl, nail manifestations included sloughing, subungual hyperkeratosis, hemorrhage, yellow discoloration, and horizontal ridging (onychorrhexis) [98].

Differential diagnosis of bullous pemphigoid of the nail includes epidermolysis bullosa acquisita (EBA), cicatricial pemphigoid, and erosive lichen planus. Indirect immunofluorescence of salt-split skin will differentiate bullous pemphigoid from EBA. Patients with EBA have blisters and erosions that characteristically heal with scarring, milia formation, and nail fragility. Cicatricial pemphigoid with nail dystrophy consisting of atrophy, longitudinal ridging (onychorrhexis), and split nails resembling lichen planus has been reported [99].

Immunohistochemistry shows that the proximal nail fold, the nail matrix, the nail bed, and the hyponychium express 220- and 180-kDa bullous pemphigoid antigens and integrin α6β4, as does the skin [100]. In patients with bullous pemphigoid and nail disease, linear deposits of C3 and immunoglobulin (Ig)M at the basement membrane zone of the proximal nail fold and the nail bed were confirmed by longitudinal nail biopsy [97]. Miyagawa et al. [101] reported coexistent linear IgG and IgA at the basement membrane zone on direct immunofluorescence.
and both IgG and IgA on indirect immunofluorescence in a 59-year-old woman with dystrophic nails who had a chronic bullous disease. This case was thought to represent an overlap of bullous pemphigoid and dermatitis herpetiformis. Electron microscopy shows clefts between the basal cells and the lamina densa [94]. Beneath the keratinocytes, the lamina densa is lost in some areas, split or detached from the keratinocytes. Plasma cells and macrophages make up the infiltrate in the dermis.

**Pemphigus**

Pemphigus refers to a group of intraepidermal autoimmune blistering diseases, the most common being pemphigus vulgaris. Nail lesions are present in about 30% of patients affected by pemphigus vulgaris [102, 103]. The severity of nail changes often parallels that of the skin [103]. Nail lesions may sometimes precede skin and mucosa findings [104]. Fingernails, especially the first, second, and third, are most commonly affected.

The anatomic location of the blister determines the clinical presentation in the nail. Involvement of the proximal nail fold is the most common presentation, with painful paronychia possibly associated with serosanguineous fluid discharge (Figs 14.69, 14.70) [93, 104–108]. Paronychia with subungual or intraungual hemorrhage can also be seen (Fig. 14.71) [109]. Paronychia may involve one or several fingers and even all 20 digits [110]. Vegetating and verrucous lesions may rarely be present on the nail folds [111]. Beau’s lines and onychomadesis eventually occur [112, 113]. Other

![Figure 14.67](image1.png) (a,b) Bullous pemphigoid: periungual involvement.

![Figure 14.68](image2.png) Bullous pemphigoid: (a) nail plate and (b) nail bed changes.
reported nail plate changes include discoloration and trachyonychia [114].

In the nail bed, subungual blisters cause onycholysis, which is often hemorrhagic. Subungual splinter hemorrhages may also be seen [115]. Primary involvement of the subungual region is rare and may result in onychomadesis with a chronic, erosive process [116, 117].

The diagnosis of pemphigus vulgaris can be made by histological identification and/or by direct immunofluorescence testing. Histopathology of the involved nail shows superbasilar acantholytic clefts leading to intraepithelial blister formation in the matrix (Fig. 14.72a) [118] and nail bed [117]. Immunohistochemistry reveals IgG and C3 in the intercellular spaces (Fig. 14.72b) [114, 118].

The prognosis of nail changes in pemphigus vulgaris is generally good with successful resolution of the nail changes with treatment [119]. Destructive changes, however, have been reported. Systemic treatment is very effective in pemphigus vulgaris and includes a combination of antiinflammatory, immunosuppressive, and/or immunomodulatory treatments [104]. In considering treatment for pemphigus vulgaris, patients who had nail involvement tended to have a poorer response to treatment with mycophenolate mofetil [120].

In Brazilian pemphigus foliaceus, established cases show initially yellowish and later dark discoloration of the nails (Vieira sign), onychorrhexis, and onycholysis [121]. Onychomadesis may occur. Pterygium, subungual hyperkeratosis, and onychogryphosis have been recorded. The nails may be rough or shiny due to permanent rubbing and scratching [122].

In pemphigus vegetans of Hallopeau, the fingernails show pustules with onychatrophy [123]. Sterile pus may be expressed from the nail folds.

Hailey–Hailey disease (familial benign pemphigus) is characterized by typical flexural crusted erosions with acantholysis on skin biopsy. Longitudinal leukonychia, prevalent in the thumbnails, is seen in more than half of the patients (Fig. 14.73) [124] and may be the first clue to...

(a) (b) (c)
the diagnosis of Hailey–Hailey disease [125]. Distal nail plate splitting and splinter hemorrhages have been described in two cases. Dermoscopy allows a better visualization of the white and red lines that may be more or less marked [126, 127].

Darier disease

Darier disease (Darier–White disease, keratosis follicularis) is an uncommon autosomal dominantly inherited disorder characterized by characterized by greasy hyperkeratotic papules in seborrheic regions, nail abnormalities, and mucous membrane changes. Nail changes are reported in up to 95% of patients [126] and they may occur in the absence of cutaneous disease [127–129]. Most commonly, two or three nails are involved but all nails may be affected. Toenails are involved less often and less severely than fingernails.

**Clinical features**

The most common nail changes seen in Darier disease are longitudinal subungual red and/or white streaks, with a feature that has suggested the name “candy-cane nails,” associated with distal wedge-shaped subungual keratoses (Figs 14.74, 14.75) [130–132]. Over time, the single or multiple red longitudinal streaks, which cross through the lunula, may characteristically develop into white ones. At the distal edge of the streak, a V-shaped notch originating in the nail bed and hyponychium is characteristic (Fig. 14.76). Here, a wedge-shaped subungual keratosis is often present that may massively thicken the nail plate in severe cases (Fig. 14.77).

Other signs of nail matrix involvement include nail plate thinning, onychorrhexis, fissuring (Fig. 14.78), fragility, and painful distal cracks and splits. A case of Darier
Disease has also been reported in which all 20 nails were lusterless, rough, ridged, and difficult to trim [133]. Keratotic papules may rarely occur in the proximal nail fold.

Nail bed disease may cause splinter hemorrhages. Hemorrhagic Darier disease, reported in 6% of Burge and Wilkinson’s patients [128], may involve the subungual tissue (Fig. 14.74b).

**Differential diagnosis**

The differential diagnosis in Darier disease includes occupational nail changes in manual laborers, lichen...
planus, X-ray damage, tuberous sclerosis, and onychomycosis [127].

Isolated distal subungal keratoses are histologically multinucleate and arise in the absence of Darier disease [134].

Keratotic papules on the dorsal nail fold may resemble acrokeratosis verruciformis of Hopf, but histology reveals Darier disease [135]. Both Darier disease and acrokeratosis verruciformis of Hopf are considered to be allelic to each other and are considered to be caused by separate defects in ATPA2 gene coding for SERCA [136]. In acrokeratosis verruciformis, the nails are pearly white in childhood (Fig. 14.79) and become horny, brown, and grooved later in life, when they may also show longitudinal nail streaks [137].

Longitudinal red or white streaks may occur in other conditions [138–142]. White and red streaks mimicking bullous Darier disease have been reported in acantholytic epidermolysis bullosa [16, 138]. The red longitudinal streak of Darier disease may also be seen in warty dyskeratoma [139, 140].

Longitudinal white bands are common in Hailey–Hailey disease but, in contrast to Darier disease, “sandwiched” red and white lines pathognomonic of Darier disease are not seen and the nail changes are asymptomatic in Hailey–Hailey disease [126, 141].

**Histopathology**

All parts of the nail unit may be affected histologically in Darier disease [135]. The nail bed findings, however, are an exception, revealing the absence of suprabasilar clefts, the presence of multinucleated epithelial giant cells, and the absence of an inflammatory infiltrate. These characteristic changes lead to the diagnosis in the rare cases when Darier disease is limited to the nails [128]. Lesions in the proximal nail fold are identical to those of the epidermis. The nail plate surface is altered when the most proximal part of the matrix is affected. Cleft formation may occur at the junction of the undersurface of the proximal nail fold and matrix. Matrix involvement results in parakeratotic cells which enter the nail plate and cause longitudinal white streaks. Multinucleate keratinocytes are included in the parakeratotic nail. The nail bed epithelium is hyperplastic. Subungal parakeratosis may be present, and may be 10–30 cells thick. The nuclei of the nail bed epithelium vary in size and shape and abundant multinucleate keratinocytes are found. Longitudinal red streaks are due to vasodilatation.

**Treatment and outcome**

Oral aromatic retinoids may improve keratotic papules of the proximal nail fold but other nail changes are not improved by treatment [143]. Baran [144] described a novel method for surgically treating hypertrophic nail plates in Darier disease by shortening the nail matrix. Successful surgical treatment utilizing an eponychial flap and full-thickness skin graft was used in a patient with dystrophic nails and nail folds subjected to repeated bouts of infection [145].

A case of human papillomavirus-induced periungual squamous cell carcinoma has been reported in a patient with Darier disease, suggesting that the altered immune status characteristic of the disease may predispose to carcinogenesis [146].

**Stevens–Johnson syndrome and erythema multiforme**

Inflammation and bulla formation in any portion of the nail unit can occur with a drug-induced reaction, such as Stevens–Johnson syndrome or erythema multiforme. Erythema and edema commonly affect the proximal nail fold and nail matrix with paronychia followed by onychomadesis (Figs 14.80, 14.81) [147]. In a patient with erythema multiforme secondary to herpes simplex, periungual erythematous papules and targetoid lesions were associated with red macules of the nail bed and lunula, evident at dermoscopy [148].

Resolution of the eruption may result in nail regrowth or scarring anonychia and pterygium [147, 149, 150].

**Toxic epidermal necrolysis**

Permanent nail dystrophy has been reported in more than 37.5% of patients with toxic epidermal necrolysis [151, 152].
Alopecia areata

Alopecia areata is an autoimmune disease characterized by patchy or total hair loss that may involve all hairy areas. Nail involvement in alopecia areata is relatively common, especially in children and in severe forms of alopecia. Nail changes may appear concomitantly or not with alopecia and are mainly seen in the fingernails. In a study on 225 patients with alopecia areata, nail changes were found in 26.2% of cases, and pitting was the most common sign [153]. In children, studies suggest a prevalence ranging from 30% to 46% [154, 155].

Clinical features

Nail matrix involvement is characteristic, with pitting as the most common nail change. Pitting has been reported in one-third to more than two-thirds of patients with alopecia areata [153, 154]. It usually involves all fingernails. Pits in alopecia areata are smaller and more regular in size and distribution along the nail plate in a so-called geometrical pattern (Figs 14.82–14.85). Compared with the broad, irregular pits in psoriasis, 7% of patients with alopecia areata exhibit finer, more regular, geometric and grid-like pitting.

Rough, friable nails may be observed (Figs 14.86, 14.87). A temporary decrease in growth in the nail matrix can lead to Beau’s lines or, occasionally, to onychomadesis, which may occur in association with an acute episode of hair loss (Figs 14.88, 14.89).
Trachyonychia or twenty-nail dystrophy, is seen in approximately 14% of cases [154]. Nails appear dull, opaque, roughened, and friable. These characteristics identify the monomorphic variant opaque trachyonychia, in which the nails appear as if they had been sandpapered in a longitudinal direction (Figs 14.90b, 14.91). The nail plate may be thinned with koilonychia. In a second monomorphic variant, all nail plates are shiny, opalescent, stippled, and longitudinally ridged (Figs 14.90c, 14.92) [156]. A third monomorphic variant is characterized by 20 thickened, brown, irregular nails masquerading as an ectodermal dysplasia or longstanding onychomycosis (Figs 14.90a, 14.93). In the polymorphic variant, any of the disorders mentioned above may be seen on different digits concurrently and the nails appear fragile and friable (Fig. 14.90d). Twenty-nail dystrophy is usually a self-limited distinct entity that has an evolution not parallel to that of the hair.
Dusky red discoloration of the lunula or of the proximal third of all the nails may be seen in alopecia areata (Fig. 14.94) [154, 157–159]. Bergner et al. [160] reported two cases of red lunulae in alopecia areata that developed several weeks after the acute onset of hair loss. The red lunulae disappeared slowly, leaving Beau’s lines. In one patient, the erythema of the lunulae migrated distally. Spotted (mottled) lunulae may be observed, with erythema similar to the color of the nail bed, and characterized as a spotty absence of whiteness (Fig. 14.95) [161]. Spotted lunulae are not specific for alopecia areata and can be seen also in nail psoriasis and lichen planus. They are reversible and come and go for no apparent reason.

True leukonychia can be seen in alopecia areata, as a result of distal nail matrix inflammatory changes. It may be punctate, transverse (Fig. 14.96), or diffuse.
Figure 14.92 Alopecia areata: shiny trachonychia.

Figure 14.93 Alopecia areata: severe trachonychia.

Figure 14.94 Alopecia areata: erythema of the lunula and of the proximal part of the nail bed.

Figure 14.95 Alopecia areata: spotted lunula.
Geometric punctate leukonychia is a rare form of leukonychia characterized by multiple small white geometrically distributed punctate spots in the nail plate (Fig. 14.97) [154]. Yellow, grey, brown, red, or opaque (asbestos nail) discoloration is much rarer.

Severe onycholysis of all nails associated with mild subungual hyperkeratosis cured after treatment with systemic steroids has been reported in a case of alopecia areata universalis (Fig. 14.98) [162].

Differential diagnosis

The differential diagnosis of the nail changes seen in alopecia areata includes lichen planus, psoriasis, and onychomycosis. Examination of the cutaneous surface (scalp, elbows, knees, gluteal cleft, etc.) should help establish a diagnosis of psoriasis. Examination of the buccal and genital mucous membranes should give supporting evidence for the diagnosis of lichen planus. When confusion exists, a nail biopsy is of great value if the disorder of the nail precedes the hair loss. When the condition is limited to the nails alone, it is impossible to determine the diagnosis of alopecia areata with certainty but a biopsy may be helpful in establishing a diagnosis of lichen planus or psoriasis. Twenty-nail dystrophy also enters the differential diagnosis; however, it is interesting to note that in some cases of “idiopathic” twenty-nail dystrophy of childhood the histological findings were reported as predominantly “eczematous,” the characteristic histopathology of alopecia areata [163].

Histopathology

Histologically, the most characteristic findings in alopecia areata appear to be spongiotic changes [163]. Histology reveals a predominantly lymphocytic infiltrate with perivascular accentuation and epidermotropism. In addition to spongiosis, spongiotic vesicles may extend up through the superficial epithelial layers. Here, proteinaceous exudate may be included in the nail, visible as homogeneous, eosinophilic, periodic acid–Schiff (PAS)-positive inclusions in the nail plate and subungual keratin. The nail plate keratin is wavy and irregularly arranged.

An eczematous appearance of the epidermis of the nail bed with vacuolated plate-staining keratinocytes of the matrix has also been reported [154].

In the histological differential diagnosis of alopecia areata, an eczematous dermatitis is very difficult to differentiate from alopecia areata of the nail when spongiosis is marked. However, in eczematous dermatitis, there is usually spongiotic dermatitis of the eponychium and outer surface of the proximal nail fold present. These features are not seen in alopecia areata.

Light and electron microscopy in alopecia areata show an architectural disorder of the corneocyte arrangement with occasional small depressions and common thin parallel pits giving a flaky appearance in the upper part of
the nail plate [164, 165]. Electron microscopy shows a cytoplasm full of vacuoles of variable size (from 140 to 1600 nm) and electron-dense deposits of material. Keratin fibers are rarefied. The intercellular spaces are larger, while the number of “ampullar dilatations” rises. The upper portion of the nail is more affected than the lower portion.

Prognosis and treatment

Spontaneous evolution of the nail changes does not usually parallel that of the hair. Intralesional corticosteroid injections quicken the resolution of the nail changes. Short courses of systemic corticosteroids may also be effective. Potent topical corticosteroids can be helpful if used for several months, but excessive use can lead to local side-effects, including premature closure of the epiphyses of the distal phalanx in the young.

Porokeratosis

Porokeratoses represent a group of acquired or hereditary dermatoses of unknown pathogenesis characterized by keratinization disorder. Different clinical forms have been identified and the most frequent are porokeratosis of Mibelli and the disseminated superficial actinic porokeratosis [166].

Porokeratosis of Mibelli is a single or several annular plaques with an elevated keratotic margin, which spreads centrifugally and most often appears on the limbs. These lesions only rarely affect the nails but, when they do, the nails may be thickened, opaque, hyperpigmented, ridged, fissured, or even partially destroyed (Fig. 14.99). Typical lesions of porokeratosis are present in the skin surrounding the nail [167, 168].

Other forms of parakeratosis may be occasionally associated with nail involvement. Dervis and Demirkesen [169] reported a case of generalized linear porokeratosis with nail dystrophy consisting of longitudinal ridging, subungual hyperkeratosis, and pterygium formation (Fig. 14.100). Unilateral congenital linear porokeratosis that extends to the proximal nail fold of the fingers causes longitudinal ridging, atrophy, and pterygium [170–172]. Onychodystrophy with pterygium has also been reported in secondary porokeratosis plantaris, palmaris et disseminata [173].

Figure 14.99 Porokeratosis of Mibelli. Courtesy of J.L. Verret.

Figure 14.100 Generalized porokeratosis.
**Acroosteolysis**

Acroosteolysis is a condition characterized by destructive distal phalangeal bone changes, which may be associated with minimal skin changes or with ischemic skin lesions that may result in digital necrosis. The condition is usually congenital but may also be acquired by exposure to strong substances, such as vinyl chloride.

Acroosteolysis is divided into groups: (i) idiopathic (familial or non-familial) and (ii) secondary. Secondary forms are associated with a number of metabolic, neuropathic, and collagen disorders.

Idiopathic acroosteolysis includes a number of different disorders that can be distinguished according to the presence or absence of genetic transmission and the association with familial renal disease, neuropathy, and ulcerative skin lesions [174–176].

In secondary acroosteolysis, many diseases that involve neurosensory loss can result in acroosteolysis. These include lepromatous leprosy, diabetic neuropathy, tabes dorsalis, syringomyelia, familial as well as non-familial mutilant ulcerative acropathy (Thévenard disease, Bureau–Barrière disease), and congenital insensitivity to pain syndrome [177, 178]. Acroosteolysis can also be observed in patients with infective, inflammatory, neoplastic, or mechanical processes. Connective tissue diseases and Raynaud phenomenon are associated. Acroosteolysis can also complicate rheumatoid arthritis or psoriatic arthropathy. Endocrinopathies, such as acromegaly and hyperparathyroidism, can cause bone resorption leading to acroosteolysis [176, 178, 179]. One important secondary association is vinyl chloride exposure. Acroosteolysis has been observed in 3–4% of workers involved in the polymerization of vinyl chloride [180]. Exposed workers developed a reversible occupational acroosteolysis that may be associated with Raynaud phenomenon and scleroderma-like skin changes. It appears that exposure alone is not responsible; a genetic susceptibility has been suggested by HLA (human leukocyte antigen) studies. Mechanical stress on the fingers of a 24-year-old guitar player produced a case of occupational acroosteolysis characterized by nail tenderness and confirmed by radiographs showing resorption of the second, third, and fourth finger of the left hand [181].

The pathogenesis of acroosteolysis is still unknown. Theories range from a noxious precipitating event to vascular occlusion precipitating the development of bone destruction [176, 182]. Genetic susceptibility also plays a role.

Radiographically, two varieties of acroosteolysis may occur together or independently: (i) a transverse acroosteolysis [183] and (ii) longitudinal acroosteolysis [178, 179]. In transverse acroosteolysis, the distal phalangeal shaft shows a transverse lytic band while the tuft and base are preserved. In longitudinal acroosteolysis, there is progressive terminal resorption of the distal end of the phalanx. The transverse radiological pattern is characteristic for vinyl chloride disease, renal osteodystrophy, idiopathic non-familial acroosteolysis, and familial acroosteolysis. It may be observed in scleroderma, hyperparathyroidism, psoriasis, neurological disorders, and frostbite. Progressive destruction of the bone produces peg-shaped phalanges.

Early changes in the skin may reveal bulbous fingertips, vasospasm, and soft tissue thickening associated with pseudoclubbing. Paresthesia and dull pain can be early manifestations of acroosteolysis. In familial acroosteolysis, pain is a conspicuous symptom. As the disease progresses, severe destruction of the digits and metacarpal or metatarsal bones may result in shortening of the distal phalanges, causing the nails to appear abnormally broad (acquired racket nails) (Fig. 14.101) [182]. Koilonychia may be observed and pincer nail deformity has occurred after traumatic acroosteolysis. In severe cases, the entire nail unit may be destroyed. The toes are frequently affected when secondary diseases are present.

![Figure 14.101](a) Acroosteolysis due to vinyl chloride disease with (b) characteristic radiological pattern. Courtesy of G. Moulin.)
characterized by neurosensory loss. Deformation and destruction of the digits are commonly accompanied by trophic changes in soft tissues and ulcerations [181, 184].

**Acrokeratoelastoidosis**

Acrokeratoelastoidosis is a skin disorder characterized by small, flesh-colored to yellowish, round to polygonal papules on the thenar and hypothenar eminences of the lateral palms and soles. The keratotic lesions of this rare condition may be seen over the knuckles and the nail folds. Van Steensel et al. [185] described a 47-year-old patient with acrokeratoelastoidosis with dystrophic nails characterized by longitudinal ridging, distal onycholysis, and pterygium formation.

**Focal acral hyperkeratosis**

Hafner and Gerstel [186] reported a 63-year-old woman with focal acral hyperkeratosis with distal dystrophy of the fingernails. Khamaysi et al. [187] reported focal acral hyperkeratosis associated with severe atrophy of the nails in all 10 fingernails in a 50-year-old woman. Histology did not show elastorrhexis and, consequently, a diagnosis of focal acral hyperkeratosis was made. However, the diagnosis in this patient appears to be a controversial point and may better represent the diagnosis of acrokeratosis verruciformis of Hopf or Darier disease [188].

**Palmoplantar keratoderma**

Patients with diffuse palmoplantar keratoderma may exhibit nail plate thickening, subungual hyperkeratosis, longitudinal fissures, and onychomadesis [189–191].

Tosti et al. [191] described two patients with both punctate palmoplantar keratoderma and psoriasis with psoriatic nail changes. Subungual hyperkeratosis was prominent, but onycholysis, splinter hemorrhages, and pitting were also present. Pathological study of the nail bed and nail matrix revealed sharply limited columns of hyperkeratosis associated with hypergranulosis and depression of the underlying nail bed epidermis. Etretinate therapy, which produced a significant improvement in the palmoplantar keratoderma, was of no apparent value in treating nail keratoderma.

Olmsted syndrome associates mutilating symmetrical palmoplantar keratoderma with periorificial keratotic plaques. Dystrophic finger and toenails have been reported as slightly whitened fingernails and toenails since birth, which changed to irregularly curved, onycholytic, hyperkeratotic nails at approximately 100 days of age [192]. Keratoderma may extend to the nail folds.

**Granuloma annulare**

Atypical changes such as pseudochromic paronychia have been observed (Fig. 14.102). Similar nail fold findings were observed in a 4-year-old girl with generalized perforating granuloma annulare [193].

**Juvenile xanthogranuloma**

Juvenile xanthogranuloma rarely affects the fingers [194–197]. Localization is under the nail and may cause nail plate thickening resembling onychogryphosis [195], partial nail plate destruction (Fig. 14.103) [194], or a pink-red nodule with telangiectasias of the proximal nail fold (Fig. 14.104) [197]. Spontaneous regression is possible.

**Erythema elevatum diutinum**

Erythema elevatum diutinum is a rare type of leukocytoclastic vasculitis characterized by red, purple, brown, or yellow papules, plaques, or nodules usually distributed

**Figure 14.102 Granuloma annulare, perforating variety. Courtesy of C.P Sanlaska.**
on the extensor surfaces of the body. Smaller plaques of the proximal nail fold have also been observed (Fig. 14.105). Subungual hemorrhage, onycholysis, and paronychia have been reported in a case associated with B-cell lymphoma [198].

Pyoderma gangrenosum

Proliferating periungual lesions due to pyoderma gangrenosum were developed in several fingernails and toenails in a woman with pyoderma gangrenosum of the leg during tapering of ciclosporin A therapy [199]. Increased dosages of ciclosporin A induced remission of the lesions.

A case of isolated subungual pyoderma gangrenosum involving the nail bed, hyponychium, and distal tip of the right toe, appearing as a purulent ulcer associated with inflammation, has been reported in 64-year-old man [200].

Vitiligo

A study on 91 patients with vitiligo showed longitudinal ridging, absence of the lunulae (Fig. 14.106), and punctate leukonychia as the most common signs [201]. Trachyonychia can be seen in patients with vitiligo,
associated or not with alopecia areata [202]. Trichrome vitiligo localized in the nail has been described in a 10-year-old boy with phototype V [203]. The second right toenail showed an irregular band of melanonychia, which disappeared after the spread of an achromatic vitiligo lesion.

Nail degloving

Nail degloving describes a possible sequela of different conditions that induce a cleavage of the dermal–epidermal junction of all the components of the nail apparatus and lead to total avulsion of the nail and the periungual tissues [35]. Causes of nail degloving described so far include acute mechanical circumferential injuries, toxic epidermal necrolysis (Lyell syndrome), digital gangrene, and dermatological conditions, i.e. epidermolysis bullosa and bullous hypertrophic nail lichen planus [35].

The clinical features of the shed nail depend on the involvement or not of the periungual tissues and on the thickness of the detached epithelium. In typical cases, the lost nail resembles the tip of a glove or a thimble. Other possible clinical features include a partially sloughed nail plate with its surrounding tissue and shedding restricted to the whole nail apparatus.

Despite the impressive appearance of nail degloving, nail regeneration with good recovery is possible if the most proximal part of the nail matrix is not shed but remains attached to the digit.

PSORIASIS

Marcel Pasch and Dimitrios Rigopoulos

Introduction/epidemiology/pathogenesis

Psoriasis is a chronic inflammatory disease that affects skin and/or nails, scalp, flexures, and joints. Nail involvement in psoriasis is common with a prevalence varying between 10% and 82% with an estimated lifetime incidence of 80–90% [204–211]. Nail psoriasis in the absence of cutaneous disease is present in 5–10% of patients with psoriasis [204, 212]. Psoriatic nail changes are more frequently encountered and severity is increased in early-onset patients, especially when psoriasis is familial [213].

The prevalence of nail psoriasis in children with psoriasis seems to be lower than that in adults, with an average prevalence of 15.7% [214] (range 7–39%) [215–219]. Congenital nail psoriasis has also been reported [220–222]. Nail pitting followed by onycholysis are the most common findings in children with nail psoriasis [217, 219, 221, 223].

It is not clear if the severity of nail disease correlates with the severity of skin psoriasis since contradicting data have been reported [210, 224–226]. Patients with psoriatic nail dystrophy are significantly older than patients with psoriasis without nail abnormalities [212]. Nail dystrophy can precede cutaneous disease but the mean age of onset of nail involvement was found to be 36 years, which was 11.5 years later than the onset of the skin symptoms [210]. Psoriatic arthritis (PsA) is associated with nail psoriasis. In a survey among 1475 patients with psoriasis, PsA was present in 46% of patients with nail involvement and in only 30% of patients without nail involvement [210]. The prevalence of nail psoriasis in patients with PsA was 75%. It is thought that arthritis may be part of the natural progression of the same disease and, if left untreated, can lead to destruction of the joint.

Clinical features

Psoriasis is a multifactorial disease with an interplay of many genetic and environmental factors, resulting in an inflammatory cascade [227]. Expression of this cascade in the nail folds, nail matrix, or nail bed causes the clinical features seen in the nail psoriasis. Because of the particular physiology and anatomy of the nail apparatus, psoriatic features have a different clinical expression in the nail than on the skin. If the epidermis of the proximal nail is involved, there may be psoriatic scaling of the proximal nail fold (Fig. 14.107) with soft tissue swelling resembling chronic paronychia [228]. Nail matrix
features include pitting, onychomadesis, leukonychia, Beau's lines, red spots in the lunula, and crumbling. Nail bed features include onycholysis, splinter hemorrhages, subungual hyperkeratosis, and oil-drop salmon patches. Pitting and onycholysis are very common in psoriatic fingernails [229–232]. Subungual hyperkeratosis and onycholysis are common in the toenails, while pitting and leukonychia are relatively rare in the toenails [212, 233, 234]. Most typically the dominant hand thumbnail and then the other nails that are most associated with hand function are affected [226, 235]. Fingernails are more often involved than toenails, but in over 60% both finger and toenails show signs of psoriasis [210].

Nail fold psoriasis

Paronychia
The epidermis of the dorsal surface of the proximal nail fold is much like its surrounding skin surface. Psoriasis here resembles the scaling, erythema, and/or pustulization of psoriasis elsewhere on the skin surface. Nail fold psoriasis is commonly found in patients with moderate to severe plaque psoriasis, with moderate to severe localized pustular psoriasis [226], and in PsA with nail involvement.

The stratum corneum of the undersurface of the proximal nail fold produces the cuticle. The chronic inflammation of the paronychia causes thickening of the free edge of the proximal nail fold with consecutive loss of cuticle and the attachment of the nail fold’s ventral surface to the underlying nail plate [236]. This allows foreign material such as dead epidermal cells, dirt, and microorganisms to enter the space beneath the nail fold, where they may aggravate inflammation, cause secondary bacterial or mycotic/candidal infection, and increase the possibility of producing a thickened and dystrophic nail plate. Pustules in the nail unit can be part of a pustular psoriasis variant and are discussed in the section “Variants of nail psoriasis.”

Nail matrix psoriasis

Proximal matrix disease can lead to superficial pits; distal matrix disease can lead to trapped parakeratotic cells in the deep plate and cause the clinical appearance of leukonychia (whitening). Alternatively, persistent disease results in sustained nail abnormalities such as loss or thickening of the nail plate.

Red lunula
Inflammation of the vessels beneath the nail may result in vessel dilation or changes in blood composition. It has been suggested that the lunula might appear spotted when there is inflammation of the intermediate or ventral matrix [207, 237, 238]. A decrease in the thickness of the nail plate may present with nail bed erythema [239].

Pitting
Psoriatic inflammation in the proximal portion of the matrix produces loose parakeratotic cells in the surface portion of the nail plate [206]. As the plate grows out, these cells are exposed to the environment and are shed, leaving a characteristic irregular punctate depression or “pit” [207]. While the parakeratotic cells can flow off the nail plate, those that remain are visible, especially with a dermoscope, as scales within the pits.

The width and depth of the pit correspond to the anatomical footprint of the inflammatory lesion. The length of the pit corresponds to the length of time the inflammation has been present.

Pits in psoriasis are usually small and shallow and irregular in size, depth, and shape (Figs 14.108, 14.109). Most pits are superficial and scattered. However, when extensive, gross abnormalities in color and texture ensue and
the nail becomes dull, rough (trachyonychia), and fragile [240]. Isolated deep pits are characteristic of psoriasis [206]. Where focal psoriasis becomes more marked, a pit may enlarge and produce a hole in the proximal nail plate overlying the lunula (elkonyxis) (see Fig. 2.32).

Pitting can occur in a variety of cutaneous and systemic diseases (see Appendix). If pitting is observed in conjunction with other abnormalities of the plate or nail bed, such as horizontal ridging in addition to pitting, a psoriatic etiology is favored. The presence of more than 20 fingernail pits suggests a psoriatic dystrophy, and more than 60 pits per person are unlikely to be found in the absence of psoriasis. Pitting is generally deeper than in lichen planus and alopecia areata [207].

**Transverse depressions**

Transverse grooves are formed at the level of the matrix in the same manner as pits but with transverse grooves, the psoriatic lesion affects a wider and compact area of the matrix. If the psoriatic lesions are of short duration and intermittent, transverse grooves and ridges within the nail plate occur, similar to transverse grooves seen in Beau's lines [241]. If the inflammation persists and involves the entire matrix, the transverse groove becomes complete and nail shedding (onychomadesis) occurs. Serial transverse depressions, especially on the thumbs, are common in psoriasis, where they may mimic “washboard” nails (Fig. 14.110).

**Longitudinal depressions**

If the focal psoriatic inflammation in the matrix persists for a longer period of time, the entire nail surface can appear longitudinally ridged [207]. This may cause fragility in the nail plate and distal splitting. Longitudinal ridges of the nail with bumps that resemble drops of melted wax are reported as common [242].

**Trachyonychia**

Another pattern of proximal matrix inflammation leads to either coarse nails or roughness (trachyonychia), which is secondary to pitting, ridging, or both [207].

**Leukonychia**

Inflammation of the mid- or distal matrix causes the accumulation of trapped parakeratotic cells within the nail plate, visualized as whitening (leukonychia) (Fig. 14.111). The white hue is due to light reflected on the nail plate on the sites of parakeratosis [211, 243].

**Chromonychia**

A silvery white color of the nail is caused by parakeratotic cells in subungual debris. Special attention should be paid to a yellow-green hue to the nail. It can sometimes be seen in psoriasis, but is also present in *Pseudomonas* infection. A yellow-green color may be produced by the accumulation of large amounts of blood glycoprotein (Fig. 14.112), commonly seen when the hyponychium and the nail bed are involved in inflammatory processes.

**Nail plate thickening**

Disordered epidermal hyperproliferation can cause thickened plaques in cutaneous psoriasis and thickened nail plates in nail psoriasis. Ultrasonography studies have shown nail plate (and nail bed) thickening also in patients without clinically apparent nail involvement [244]. It is possible that much of the nail thickening is
linked to an aberrant response to repeated microtrauma of the nail matrix and/or the distal interphalangeal (DIP) joints.

**Dystrophic crumbling nail plate**

The level of matrix psoriatic involvement produces different nail plate changes, but when the whole matrix is affected the nail plate becomes off-white and crumbles [206] (Fig. 14.113). Crumbling is particular and frequent in patients with DIP joint arthritis [228].

**Nail bed psoriasis**

**Oil-dropping sign**

Psoriasis lesions in the nail bed appear as irregular “salmon-colored,” “oil-drop” patches of various sizes and variable duration and are observed through the nail plate [245] (Fig. 14.114). Infiltration of lymphocytes, parakeratotic cells, neutrophils, and glycoprotein deposition may be responsible for its characteristic color [245]. It might be visible in the central nail bed, or around the onycholysis,
near the free nail edge. When the “oil-drop” patch affects the hyponychium medially or laterally, the plate separates from the nail bed and onycholysis occurs.

**Onycholysis**

The development of distal or lateral nail bed “oil-drop” patches and desquamation of parakeratotic cells at the hyponychium may decrease the adhesion of the nail plate to the nail bed and cause separation of the nail plate from the nail bed (onycholysis) [246]. The yellow color of the onycholytic nail results from the combination of air between the nail bed and dislodged nail plate, and from the accumulation of keratinocytes. In psoriatic onycholysis, the undersurface of the nail plate retains nail bed cells. In the toenails, onycholysis is frequently associated with subungual hyperkeratosis [247]. Trauma and irritation exacerbate onycholysis partially because of the Koebner phenomenon. Onycholysis surrounded by a reddish-yellow margin, visible between the normal pink nail bed and the whitish separated area, is highly suggestive of psoriasis [247]. Onycholysis alone without previous nail injury is suggestive of psoriasis [248].

**Splinter hemorrhages**

Capillary injury in the longitudinally oriented epidermal–dermal ridges manifests clinically as small linear hemorrhages resembling wood “splinters” in the nail. Most commonly precipitated by trauma, splinter hemorrhages frequently occur under the distal third of the nail plate in psoriasis where nail plate dystrophy and capillary fragility are predisposing factors [249]. Splinter hemorrhages (Fig. 14.115) were assumed to be less prevalent than other nail findings in psoriasis [224] but using dermoscopy they were found to be present in 94% of patients with nail psoriasis and in 37% of healthy controls [229]. They are more commonly seen in fingernail psoriasis than in toenail psoriasis [224].

**Subungual hyperkeratosis**

Nail bed hyperkeratosis with accumulation of keratinocytes under the nail plate is referred to as subungual hyperkeratosis. It involves the distal nail bed and hyponychium. The extent to which the nail plate is raised off the nail bed depends on the degree of local psoriatic activity. Overcurvature of one or more nails may be seen occasionally. Subungual hyperkeratosis can vary from yellow to white in color [206]. In psoriasis, subungual hyperkeratosis is more often a less common silvery white color owing to the air that enters the elevated distal end of the nail plate but may change if there is a secondary infection; in other conditions subungual hyperkeratosis takes on a more yellowish, “greasy” appearance, possibly because of a more pronounced inflammatory response and deposition of serum or serum glycoprotein [207].

The nail bed alters its keratin profile in psoriasis. Normally the keratins of terminal differentiation, K1 and K10, are absent in the healthy nail bed. However, these keratins are expressed in psoriatic nail bed combined with an increase in epidermal turnover at the same site [250]. These changes underlie the clinical features of subungual hyperkeratosis.
Considerations in the diagnosis of nail psoriasis

In making the diagnosis of psoriasis, there are many helpful clinical clues to be considered. A search for associated signs of psoriasis at other cutaneous sites may be extremely helpful.

Laboratory tests are also helpful. In patients with psoriasis with onycholysis and subungual hyperkeratosis, it is imperative to exclude the possibility of a fungal nail infection. Radiographs can be used to look for psoriatic changes in the DIP joint. Different forms of nail plate and nail bed biopsy have been described to help distinguish between onychomycosis and nail psoriasis [251, 252]. Patients with psoriasis are more likely to develop onychomycosis [253], so a positive fungal test does not exclude the presence of nail psoriasis. A nail punch or excisional biopsy with or without nail plate avulsion can confirm or exclude the possibility of psoriasis (Figs 14.116, 14.117) [254].

Variants of nail psoriasis

Sterile pustular conditions

The nomenclature is confusing with regard to sterile pustular conditions of the nail, perhaps because of the fact that there is considerable overlap between acrodermatitis continua of Hallopeau (ACH), acropustulosis repens, palmoplantar pustulosis, pustular bacterid, and acute generalized pustular psoriasis. There is controversy regarding whether these conditions are separate entities or are on a continuum with pustular psoriasis.

Biopsy may be the only way to confirm the general nature of a pustular process in the nail even when no pustules can be seen clinically.
coalesce to form lakes of pus. The nail may gradually shed and be replaced by a mixture of scale and pustules of the nail bed. Severe acral pustular inflammation in ACH may involve entire digits with loss of the tips of digits and nails [256]. Acral pustular psoriasis has been reported with resorptive osteolysis described as a "deep Koebner phenomenon" (Figs 14.119, 14.120) [257, 258]. Marked skin and subcutaneous tissue atrophy with "tuft" osteolysis may occur independently of acropustulosis and arthritis in psoriasis [259].

**Palmoplantar pustulosis** (Fig. 14.121) is a pustular papulosquamous condition in which cutaneous involvement is limited to the palms and soles with variable nail involvement.

There is considerable controversy as to whether subungual pustular nail disease in patients with palmoplantar pustulosis points toward palmoplantar pustulosis or, because of the pustular nail changes, toward ACH [260–262]. About 30% of patients with palmoplantar pustulosis have nail involvement [261, 262]. Subungual pustulation was observed in 14%, and may progress to nail destruction in a minority of patients [262]. Other nail signs are superficial abnormalities (71%), pitting (43%), curvature abnormalities (7%), discolorations (21%), onycholysis (50%), and nail destruction (39%).

**Acropustulosis repens** is a form of acropustulosis with few lesions, evolving with remissions and relapses, with a much more benign course than ACH [263]. Only six patients have been reported, all of them by Proença [263]. It can be differentiated from ACH using the following diagnostic criteria: (i) it is a benign condition with spontaneous healing, (ii) the pustules are located on the hyponychium or nail bed, (iii) pustules can be single or occur in small groups, (iv) they recur in flares, with normalization of the nail unit during the periods of remission, (v) the pustules are sterile, and (vi) microscopic study shows a subcorneal pustule filled with neutrophils (spongiform aspect is rare). Like ACH the eruptions usually affect only one finger at a time.

**SAPHO syndrome** (synovitis, acne, pustulosis, hyperostosis, and osteitis), an acronym introduced by Chamot and Kahn [264], may be associated with subungual pustules [265].
Treatment of pustular nail psoriasis often differs from that of other forms of nail psoriasis, and will be discussed here. It may involve therapy for a precipitating infection in (acute) palmoplantar pustulosis [262]. Topical medications as monotherapy, such as corticosteroids [266, 267], calcipotriol [268–270], and tacrolimus [271, 272], or in combinations such as the two-compound product containing calcipotriol and betamethasone dipropionate [273], calcitriol and tacrolimus 0.1% [274], and a sequential combination of calcipotriol and tacrolimus ointments [272] have been used with helpful results. Oral tetracycline and topical betamethasone valerate with occlusive dressing were reported effective in severe inflammatory ACH [266]. The TNF blocking agents etanercept, adalimumab, and infliximab appear to be very beneficial in pustular variants [275–286], but reports have associated these therapies with de novo paradoxical development of psoriasis, specifically palmoplantar pustulosis, in patients undergoing treatment for unrelated conditions [287, 288]. In one case infliximab was not effective but skin cleared with a combination of adalimumab with high-dose acitretin [289]. Ustekinumab has been used successfully as monotherapy [290], including in a case of TNF-antagonist-induced palmoplantar pustulosis [291].

The TNF blocking agents etanercept, adalimumab, and infliximab appear to be very beneficial in pustular variants [275–286], but reports have associated these therapies with de novo paradoxical development of psoriasis, specifically palmoplantar pustulosis, in patients undergoing treatment for unrelated conditions [287, 288]. In one case infliximab was not effective but skin cleared with a combination of adalimumab with high-dose acitretin [289]. Ustekinumab has been used successfully as monotherapy [290], including in a case of TNF-antagonist-induced palmoplantar pustulosis [291].

**Acral psoriasiform hemispherical papulosis**

Acral psoriasiform hemispherical papulosis (Fig. 14.122) is probably a clinical variant of psoriasis. It presents as symmetrically distributed, grouped erythematous cornified hemispherical papules on the fingertips and toes. Nail plates may be thickened and rough and accompanied by subungual hyperkeratosis.

**Psoriatic onychopachydermoperiostitis**

Psoriatic onychopachydermoperiostitis (POPP) (Fig. 14.123) is a variant of PsA characterized by involvement of the toes (usually the great toe), psoriatic onychodystrophy (usually onycholysis), painful soft tissue swelling at the end of the digit, and osteoperiostitis of the distal phalanx with a normal DIP joint [292–296]. It was recognized early as pain and swelling of the digit pulp, nail dystrophy, osteolysis, and absence of joint involvement [258, 297]. Classic psoriatic lesions may be present or absent, and pain may lead to severe functional and quality of life impairment [298]. POPP has also been reported in the fingers [299, 300] as well as unilaterally in one great toe [301].

Methotrexate is the treatment of choice for POPP [302–304]. Anti-TNF-α biological agents may also be beneficial [298, 302].

**Reactive arthritis**

Reactive arthritis (previously known as Reiter syndrome) is characterized by the classic triad of conjunctivitis, urethritis, and arthritis. It is associated most commonly with infections, especially urogenital and gastrointestinal [305]. It is more common in men and familial cases are reported. Pediatric cases with nail involvement have been reported [306]. As in PsA, the ligament and tendon insertion into bone (enthesis) appears important [305]. In reactive arthritis, enthesitis may be the predominant symptom.
Nail changes occur in 20–30% of patients with reactive arthritis [305]. They may be indistinguishable from the changes in psoriasis both clinically and histologically (Fig. 14.124a). Pitting may be deep and punched-out lesions can occur and may be secondary to inflammation of the proximal nail fold. The nails may be greenish yellow or brownish red in coloration. Small yellow pustules may develop and slowly enlarge beneath the nail, often near the lunula, later turning dry and brown. Terry nails may be observed [306, 307].

Treatment includes PUVA and retinoids (Fig. 14.124b). Combined treatment using methotrexate [308], retinoid, and prednisolone has been suggested. Antibiotics, steroids, and non-steroidal anti-inflammatory drugs are of no benefit in reactive arthritis.

Differential diagnosis

Nail psoriasis might accompany skin psoriasis or the nails might be the sole presentation. Nail signs might contribute in the diagnosis in patients with both nail and cutaneous involvement when considering disorders with similar clinical signs. Pits, a symptom not restricted to nail psoriasis, in this case are characteristically deep. Subungual hyperkeratosis is common in several nail disorders, but in psoriasis it usually is silvery white in color. Psoriatic onycholysis is characterized by the presence of an erythematous rim surrounding the area of onycholysis in the fingernails [309]. Splinter hemorrhages in the distal third of the nail can be found in psoriasis but also in many healthy individuals [228]. The “oil-drop sign” and the red lunula spots are more specific for psoriatic nail disease [244] but red lunula spots can also be seen in alopecia areata.

Diseases which share several clinical features of psoriatic nail disease include:

- sterile pustular conditions: palmoplantar pustulosis, ACH, pustular bacterid, and acute generalized pustular psoriasis
- reactive arthritis
- pityriasis rubra pilaris
- parakeratosis pustulosa
- Norwegian scabies
- acrokeratosis paraneoplastica of Bazex
- psoriasiform acral dermatitis
- punctate keratoderma
- lichen nitidus with nail dystrophy
- hyponychial dermatitis
- Sézary syndrome.

Associations

Underlying bone pathology can be seen in patients with psoriatic nail dystrophy. In a study in patients with psoriatic nail dystrophy and without symptomatic PsA, Serarslan et al. [310] found that terminal phalanx bone tuft radiographic changes were significantly higher in patients with nail dystrophy and correlated with psoriasis severity. Magnetic resonance imaging was able to detect phalangeal bone edema in patients with PsA who were prone to develop onycholysis and subungual hyperkeratosis [311]. An association with other autoimmune conditions has also been suggested [312], in particular with inflammatory bowel disease [313] and with multiple sclerosis [314].

Nail psoriasis is mostly considered a risk factor for onychomycosis [315–317] but some authors report that the prevalence of onychomycosis in patients with psoriasis is not higher than that in the general population [318, 319]. A recent systematic review on this topic reported an average prevalence of onychomycosis of 18.0% in patients with psoriasis [253], which seemed to be increased compared with control groups and literature on a healthy population. Exacerbation of nail psoriasis in
patients with onychomycosis due to the Koebner phenomenon has been suggested [320]. It appears appropriate that mycological investigation is indicated in all patients with suspected nail psoriasis.

Imaging techniques

These are discussed in Chapters 3–8.

Quality of life

Psoriatic nail disease affects quality of life (QoL) and results in significantly more days off work than in patients without any nail involvement [321]. Recent studies have proven that patients with nail psoriasis have a significantly lower QoL than patients with skin psoriasis only [322–325]. Patients report that nail psoriasis is bothersome (86%), unsightly (87%), and painful (59%) [326]. Nail psoriasis has been shown to interfere with patients’ mental, physical, and, most pronounced, social well-being [327], in particular in females [326, 328]. Furthermore, patients with involvement of nails were found to be more negatively impacted on intimacy than without nail involvement [329].

When comparing the burden on QoL between different nail disorders, patients with nail psoriasis experience similar impairment in their QoL by psoriasis, onychomycosis, chromonychia, and trauma [330].

Severity scales

Scoring systems are indispensable for the evaluation of the severity of disease and to monitor treatment response. Using one and the same scoring system at fixed time points is also a prerequisite to compare results of different studies. The most common methods to determine disease severity in psoriasis, such as the psoriasis area and severity index (PASI), do not include specific features of nail psoriasis. In past years, several scoring systems have been proposed to assess nail psoriasis severity [331–339]. Despite the importance of a generally accepted scoring system, there is a lack of consensus on the most appropriate of these measures [338, 340, 341].

Management of nail psoriasis

Introduction and general advice

In contrast to the recent advances in treatment strategies for cutaneous psoriasis, treatment of nail psoriasis remains difficult, with often temporary efficacy and little help from guidelines or good-quality evidence or trial data [342]. Clinicians as well as patients often find the treatment of nail psoriasis to be impractical, difficult, unrewarding, and unsatisfactory. There are, however, a range of therapies that have the potential for success (Table 14.1), and a positive and thorough approach will usually result in some improvement.

The approach to a patient with nail psoriasis should be individualized, and this depends on the part of the nail that is affected (location), the association of skin and/or joint lesions, impact on QoL, comorbidities, age and gender of the patient, and productivity or ability to work. Simple guidelines always remain of utmost importance (Table 14.2). In those with minimal disease and in children, it is usually best to avoid anything but the most simple therapies and to avoid the use of long-term potent topical corticosteroids with their potential sequelae [343–345].

Therapeutic regimens range from simple emollient and steroid applications to injected corticosteroid, systemic agents, and biologics (Table 14.1). In nail matrix psoriasis, such as pitting and ridging in which there is also nail fold inflammation, lesions may clear by treating the nail folds alone [346]. In nail bed disease such as onycholysis and subungual hyperkeratosis, topical treatments should be applied as close to the bed as possible after curettage or clipping back the nail plate even beyond the hyponychium [207]. Clipping of the nail is not required in order to achieve optimal results in subungual hyperkeratosis. In general, topical corticosteroids and/or vitamin D3 analogues reduce subungual hyperkeratosis, and tazarotene may improve onycholysis and pitting. Intralesional corticosteroids in the proximal nail fold are efficacious in matrix disease but may not help onycholysis. Most systemic agents and biologics are efficacious in both matrix and bed psoriasis but may be costly and have potential systemic adverse effects. They may be best reserved for nail patients who experience a great impact on QoL or with more widespread cutaneous or joint disease.

Topical therapy

Topical therapies are mainly for application to the base of the nail. At this site they may treat psoriasis of the nail fold and penetrate through to the underlying matrix to a limited extent. Efficacy of topical medications improves with the use of an occlusive glove or dressing.

Corticosteroid

In nail psoriasis, potent and superpotent corticosteroids are used frequently and appear to be more effective in nail matrix psoriasis than in nail bed psoriasis. They may be used with or without occlusive dressings such as non-porous tape or plastic gloves for short repeated periods. Overnight application at the proximal nail fold of
Table 14.1 Available treatments for nail psoriasis [343].

<table>
<thead>
<tr>
<th>Category</th>
<th>Therapy</th>
<th>References</th>
</tr>
</thead>
<tbody>
<tr>
<td>Steroid</td>
<td>Topical</td>
<td>[347–351]</td>
</tr>
<tr>
<td></td>
<td>Injected local</td>
<td>[352–357, 475]</td>
</tr>
<tr>
<td></td>
<td>Injected systemic</td>
<td>[358]</td>
</tr>
<tr>
<td>Vitamin D derivates</td>
<td>Topical calcipotriol</td>
<td>[268, 347, 359–361]</td>
</tr>
<tr>
<td></td>
<td>Topical calcitriol</td>
<td>[362]</td>
</tr>
<tr>
<td></td>
<td>Topical tacalcitol</td>
<td>[363, 468]</td>
</tr>
<tr>
<td>5-Fluorouracil</td>
<td>Topical</td>
<td>[337, 364–367]</td>
</tr>
<tr>
<td>Calcineurin inhibitors</td>
<td>Topical tacrolimus</td>
<td>[368]</td>
</tr>
<tr>
<td></td>
<td>Topical ciclosporin</td>
<td>[369, 370]</td>
</tr>
<tr>
<td></td>
<td>Systemic ciclosporin</td>
<td>[371–376]</td>
</tr>
<tr>
<td>Apremilast</td>
<td>Systemic</td>
<td>[377–380]</td>
</tr>
<tr>
<td>Methotrexate</td>
<td>Injected local</td>
<td>[381]</td>
</tr>
<tr>
<td></td>
<td>Systemic</td>
<td>[373, 376, 383, 384]</td>
</tr>
<tr>
<td>Retinoids</td>
<td>Topical tazarotene</td>
<td>[349, 385–388]</td>
</tr>
<tr>
<td></td>
<td>Systemic</td>
<td>[359, 371, 373, 382, 383, 389, 390]</td>
</tr>
<tr>
<td>Biologics</td>
<td>Adalimumab</td>
<td>[373, 375, 391–404]</td>
</tr>
<tr>
<td></td>
<td>Briakinumab</td>
<td>[384]</td>
</tr>
<tr>
<td></td>
<td>Certolizumab pegol</td>
<td>[405]</td>
</tr>
<tr>
<td></td>
<td>Etanercept</td>
<td>[373, 400–403, 406–412]</td>
</tr>
<tr>
<td></td>
<td>Golimumab</td>
<td>[413]</td>
</tr>
<tr>
<td></td>
<td>Infliximab</td>
<td>[236, 414–423]</td>
</tr>
<tr>
<td></td>
<td>Ixekizumab</td>
<td>[424–428]</td>
</tr>
<tr>
<td></td>
<td>Secukinumab</td>
<td>[429]</td>
</tr>
<tr>
<td></td>
<td>Ustekinumab</td>
<td>[400, 430–436]</td>
</tr>
<tr>
<td>Combination therapies</td>
<td>Topical corticosteroid and calcipotriol</td>
<td>[437–439]</td>
</tr>
<tr>
<td></td>
<td>Topical corticosteroid and topical tacalcitol</td>
<td>[440, 469]</td>
</tr>
<tr>
<td></td>
<td>Topical calcipotriol and systemic ciclosporin</td>
<td>[441]</td>
</tr>
<tr>
<td></td>
<td>Adalimumab and ciclosporin</td>
<td>[375]</td>
</tr>
<tr>
<td></td>
<td>Adalimumab and topical betamethasone/calcipotriol</td>
<td>[395, 396]</td>
</tr>
<tr>
<td>Others</td>
<td>Colloidal silicic acid</td>
<td>[442]</td>
</tr>
<tr>
<td></td>
<td>Nimesulide</td>
<td>[267]</td>
</tr>
<tr>
<td></td>
<td>Dithranol</td>
<td>[443]</td>
</tr>
<tr>
<td></td>
<td>Indigo naturalis oil</td>
<td>[444–446]</td>
</tr>
<tr>
<td></td>
<td>Fumaric acid</td>
<td>[447]</td>
</tr>
<tr>
<td></td>
<td>Sulfasalazine</td>
<td>[448]</td>
</tr>
<tr>
<td></td>
<td>Leflunomide</td>
<td>[449]</td>
</tr>
<tr>
<td></td>
<td>Bone marrow transplant</td>
<td>[450]</td>
</tr>
<tr>
<td>PUVA</td>
<td>Topical psoralen</td>
<td>[451]</td>
</tr>
<tr>
<td></td>
<td>Systemic psoralen</td>
<td>[373, 452]</td>
</tr>
<tr>
<td>UVB</td>
<td>Narrow band</td>
<td>[373, 383]</td>
</tr>
<tr>
<td></td>
<td>Excimer laser</td>
<td>[453]</td>
</tr>
<tr>
<td>Radiation therapy</td>
<td>Grenz rays</td>
<td>[454, 455]</td>
</tr>
<tr>
<td></td>
<td>Electron beam therapy</td>
<td>[456]</td>
</tr>
<tr>
<td></td>
<td>Superficial radiotherapy</td>
<td>[457–459]</td>
</tr>
<tr>
<td>Laser therapy</td>
<td>Pulsed dye laser (595 nm)</td>
<td>[388, 460–464]</td>
</tr>
</tbody>
</table>

PUVA, psoralen ultraviolet A; UVB, ultraviolet B.
high-potency topical corticosteroids has been shown to help pitting and surface ridging, especially if there is concurrent nail fold inflammation [207].

In spite of the long history of corticosteroids in the treatment of nail psoriasis, there have been only a few formal trials of their efficacy [347–359]. However, these studies did find positive effects on subungual hyperkeratosis, salmon patches, pitting, and onycholysis after 12–20 weeks of use. Formulations with corticosteroids in a nail lacquer have been studied several times but are not yet commercially available [350, 465, 466]. The symptoms that responded best to therapy were onycholysis and pitting. Iontophoresis was used in order to increase dexamethasone absorption in patients with nail psoriasis. An extraordinary 81% improvement in the Nail Psoriasis Severity Index (NAPSI) was reported in all patients who tolerated well the method [467].

Caution must be exercised with the long-term use of potent corticosteroids. Persistent use of these agents can result in skin atrophy and tapering of the distal phalanx on the treated digit with as little as 1 month of treatment using a high-potency topical corticosteroid [343–345].

5-Fluorouracil (5-FU) has had variable results in the treatment of nail psoriasis [337, 365, 367] and is not used commonly in nail psoriasis because of its frequent adverse effects and doubtful efficacy [470].

Calcineurin inhibitors: tacrolimus
In one study tacrolimus was proven to be effective for both nail matrix and bed signs after application on the nail folds at bedtime, without occlusion [368].
Tazarotene

Tazarotene has been investigated in nail psoriasis in a number of clinical trials [385, 386]. From these studies, tazarotene under occlusion appears to be effective for nail bed signs of psoriasis. The use may be limited by the relatively frequently occurring side effects such as erythema, irritation, desquamation, and paronychia.

Others topical treatments

Dithranol

Dithranol may have some beneficial effects in nail psoriasis [443] but its use is limited by adverse effects [207, 443].

Indigo naturalis oil

A refined formulation of indigo naturalis oil extract (0.1 mg/mL and 0.2 mg/mL) has been investigated in nail psoriasis in four studies [444–446, 471]. All these studies showed improvement of nail psoriasis after daily application onto the lateral nail folds, eponychium, and hyponychium.

Intralesional therapy

Corticosteroid

Intralesional corticosteroid injection into the area of the nail matrix and/or bed in nail psoriasis is effective. Its use has been more extensively documented than many of the alternative treatments used. Both the antiinflammatory and antiproliferative effects of corticosteroids make it an excellent choice [207]. Local penetrating doses of steroid into a digit are given by 28–30-gauge needle injection. Precooling the digit with an ice pack, liquid nitrogen, or a refrigerant spray may help with the discomfort of injection [472]. Some injectors use local anesthesia in the form of a local or digital block; others do not. The need for local anesthetic will depend on the patient, the technique, the size of the needle, the volume to be injected, and the patient’s pain tolerance.

The proximal nail fold has been used for injection in the case of matrix psoriasis, but the preferred treatment is at the lateral nail folds: more proximal for matrix psoriasis and more distal for nail bed psoriasis. In the lateral nail fold, the goal is to deliver the corticosteroid to the dermis of the matrix and nail bed by injecting the subcutaneous tissue lateral to the matrix and/or nail bed, allowing the corticosteroid to diffuse to the targeted area. For nail bed and matrix disease, an injection in each digit bilaterally at the lateral nail fold of a total volume per injection of 0.1 mL (total per finger = 0.4 mL) is used.

The corticosteroid of choice is usually a suspension of triamcinolone acetonide, which can be diluted with normal saline or a local anesthetic and is used in varying concentrations and frequencies of application. The recommended protocols of treatment differ considerably. Initially injections of triamcinolone acetonide (5 mg/mL) were given monthly for 6 months in the proximal nail fold, followed by a further four injections over the next 6 months and then every 2 months for the final 6–12-month period [353, 356, 473, 474]. More recent publications recommend a higher concentration of triamcinolone acetonide (10 mg/mL), 0.1 mL given in each of four periungual sites ensuring symmetrical delivery of steroid to nail matrix and nail bed, and administered less frequently such as every 2 months [352, 357]. Clinical results of this modified regimen were investigated in two studies suggesting improved efficacy on signs of nail bed psoriasis [352, 357]. Pits or ridges [355, 356, 473] and nail thickening and subungual hyperkeratosis [352] are the most steroid-responsive nail changes. Onycholysis and, according to some authors, pitting are the most resistant. Improvement in matrix and bed NAPSI of about 50% has been reported [475].

The main disadvantage of intralesional corticosteroid injection is pain. Adverse effects of these procedures are well known: short-term paresthesia [352, 353, 357], focal pain that may last for several months [354, 358], perungual hypopigmentation [476], and hematoma formation is rather common, up to 20%, but asymptomatic [357]. Loss of nail plate was seen in 9% in one study [357]. Occasionally nail fold atrophy can be encountered, but is often reversible. Chronic topical therapy can lead to complications of a “disappearing digit” [345] with atrophy of the underlying phalanx [343]. Rupture of the extensor tendon has also been reported after local injection of steroids [477, 478].

Methotrexate

Intralesional use of methotrexate is not a generally accepted treatment in nail psoriasis.

Non-pharmacological treatments

Phototherapy

All phototherapeutic options with light of varying wavelengths and in combination with oral and topical photosensitizers (psoralens in PUVA or aminolevulinic acid in photodynamic therapy) have been investigated in nail psoriasis [479] but are not used routinely. Photodynamic therapy has been shown ineffective in nail psoriasis, both as a monotherapy and as a pretreatment in pulsed dye laser treatment [460]. PUVA phototherapy with either oral or topical psoralens appears to be effective in both nail bed and nail matrix disease [373, 451, 452]. Narrow-band ultraviolet B (UVB) B therapy, also with an excimer laser, appears to be much less effective or not effective at all in treating nail psoriasis [373, 383, 453]. Positive results of ultraviolet A (UVA) and narrow-band UVB are surprising considering that the penetration of UVA light through the fingernails is only 1.65%, and UVB is completely blocked [480].
Radiotherapy
Radiotherapy is rarely used in daily clinical care of patients with nail psoriasis.

Grenz rays
Grenz rays, a superficial form of radiation therapy that penetrates the skin only, has been found to be effective when psoriatic nails were of normal thickness [454, 455].

Superficial radiotherapy
Several dose regimens of superficial radiotherapy have been reported to be beneficial [457, 458]. Superficial radiotherapy may be considered in selected patients, especially older individuals. The total dose per lifetime should be monitored and should not exceed 10 Gy (1000 rad).

Electron beam therapy
Electron beam therapy can penetrate the nail matrix and bed, but treatment may be unrewarding.

Laser therapy
A positive clinical effect of the pulsed dye laser (595 nm) is supposed to be its effect on angiogenesis and vascularity within the psoriatic nail unit. An increasing number of case reports and clinical studies have been reported [388, 460–464]. Results in these publications are rather contradictory. The major side-effect of pulsed dye laser treatment is pain, which lasts for 24 h. Other potential adverse events are petechiae and hyperpigmentation in 30% of the nail folds, in virtually all patients. Pain but also petechiae are worse if a longer pulse duration is used.

Systemic therapy
Systemic treatments offer a valuable alternative in patients with moderate to severe plaque psoriasis, PsA, and those who have severe nail disease with a major impact on QoL, pain, or on daily life and profession. The choice for optimal systemic treatment in a patient also depends on the presence of other expressions of psoriasis, other diseases of the patient, the patient’s and doctor’s preferences and experiences, long-term safety, side-effects, and costs of treatment.

Conventional systemic therapy
Retinoids
Acitretin and etretinate reduce keratinocyte proliferation and control inflammation [207], and can be used for years in patients who can tolerate their side-effects, such as cheilitis, dry mouth, and skin exfoliation [481]. The effect of systemic retinoid therapy on the nail is strongly dose dependent and, at doses used for psoriasis of the skin, it can worsen nail fragility, reduce nail thickness, and induce pseudopyogenic-type granuloma and anonychia-like lesions [371]. Thinning of nails of normal thickness may exacerbate pitting and onycholysis [249, 382]. Therefore doses used for nail disease (acitretin between 0.2 and 0.3 mg/kg/day) are often lower than those used in plaque psoriasis.

The position of retinoids in treatment of nail psoriasis is that of rather slow-acting compounds with moderate efficacy and action, in particular on nail bed signs of psoriasis [371, 373, 382, 383, 389, 390, 482]. Studies indicate that a NAPSI improvement of 40–50% may be expected after prolonged use [375, 392].

Methotrexate
Only a few studies using methotrexate to treat nail psoriasis exist. These studies showed efficacy but significantly less than most biologics [373, 376, 383, 384]. One trial comparing methotrexate and ciclosporin in nail psoriasis did not show statistically significant overall NAPSI differences between both drugs [376], but methotrexate was effective against matrix psoriasis and ciclosporin against bed psoriasis. Methotrexate efficacy to treat nail psoriasis has also been compared with the biologic briakinumab [384]. Target NAPSI improved by 38% in methotrexate-treated patients and by 56% in briakinumab-treated patients.

Ciclosporin
The calcineurin inhibitor ciclosporin shows a reasonable efficacy in treatment of both nail bed and nail matrix signs of psoriasis [371–375, 441].

In a randomized controlled trial ciclosporin resulted in a statistically significant improvement of 46% in nail disease from baseline [371]. Ciclosporin has also been used as combination therapy. Ciclosporin with topical calcipotriol showed better and longer improvement in subungual hyperkeratosis, onycholysis, and pitting [441].

The efficacy of ciclosporin has also been compared with methotrexate [376]. The use of ciclosporin may be limited by the relative high rates of relevant side-effects. The most serious long-term adverse reactions are development of renal failure and several malignancies. For this reason it is often used only for a period of 6–12 months.

Apremilast
Apremilast has been investigated in two randomized controlled trials, ESTEEM 1 and ESTEEM 2, in which nail psoriasis was a secondary endpoint [377–380]. After 52 weeks of treatment, NAPSI improvement was approximately 60% in both studies. Both nail matrix and nail bed psoriasis improved significantly. The too liberal definition of nail psoriasis in these studies (NAPSI ≥1) makes it hard to draw conclusions about the efficacy in clinically relevant nail psoriasis.
Other conventional systemic therapies: fumaric acid esters, sulfasalazine, and leflunomide
Fumaric acid esters, sulfasalazine, and leflunomide have been investigated in nail psoriasis but cannot be advised for this indication.

Biologics
Most biologics have been studied for their efficacy in nail psoriasis, and all investigated anti-TNF-α biologics have been shown to be effective treatments for nail psoriasis. More recently, also anti-interleukin (IL)-17 antibodies and anti-IL-12/23 monoclonal antibodies have proven to be excellent treatments for nail psoriasis. Results with all biologics appear to be in the same range [341]. In general, nail responses are slow but continue to improve, lagging behind cutaneous responses over time. The onset of response in nail psoriasis mostly is noticeable after about 12 weeks; further improvement or even complete clearance can be seen through to 1 year of treatment. Overall, patients with greater skin or joint responses also demonstrated better nail responses. On the other hand, presence of nail disease was not shown to predict a good response of PsA [394], and improvement of nail psoriasis by a biologic was independent from presence or absence of PsA [392].

Infliximab
Several studies have proven the beneficial effect of infliximab on nail psoriasis, in both patients with PsA and those with plaque psoriasis with severe nail psoriasis at baseline. It appears equally effective in nail bed and nail matrix psoriasis [235, 416]. Patients with a high PASI response have a more rapid and profound nail response than patients with a poorer PASI response [483]. Also QoL improves during infliximab treatment in nail psoriasis [414]. A retrospective real-life study in patients with rather severe nail psoriasis showed excellent results with complete clearance in 10% of patients [422]. A study comparing the incidence of onychomycosis in patients treated with infliximab, etanercept, adalimumab, and controls has shown twice as much fungal infection in the nails of patients with psoriasis on infliximab as in the nails of patients on etanercept, adalimumab, and controls [412].

Adalimumab
The first study on adalimumab in nail psoriasis was an open label study in patients with mild to moderate nail psoriasis [392]. After 24 weeks of treatment, the fingernail NAPSI had improved by 85%. No differences in efficacy were seen between patients with plaque psoriasis only and those with both plaque psoriasis and PsA. Other open label studies confirmed the efficacy of adalimumab on nail disease in patients with PsA but at a lower level [393, 394]. Further findings were that nail improvement was independent from prior treatment with infliximab and/or etanercept, and that presence of nail disease was unable to predict good response in arthritis. The BELIEVE and REACH studies in patients with plaque psoriasis confirmed efficacy on nail disease in randomized controlled trials [395–398, 404]. Daily practice studies were published by Sola-Ortigosa et al. [399], by Bardazzi et al. [400], and by Kyriakou [401]. These studies reported NAPSI improvement ranging from 57% [399] to 94% [400]. The efficacy of adalimumab in trials comparing several systemic and biologic therapies is in the same range as in the above mentioned studies [373, 375, 402, 403].

Etanercept
Several case reports [406, 409, 410] and a retrospective and observational study [407] claimed efficacy of etanercept in nail psoriasis. A post hoc analysis of a randomized controlled trial showed NAPSI improvement of 51% after prolonged use [408]. Patients with nail psoriasis also showed significant and clinically meaningful improvement in QoL with etanercept [408, 411]. One dose-finding study was unable to show differences between etanercept 50 mg twice weekly for 12 weeks followed by 50 mg once weekly for another 12 weeks and etanercept 50 mg once weekly for 24 weeks [411]. Target NAPSI improved by 72% and 76%, respectively. Daily practice studies were published by several authors, and showed NAPSI improvements up to 94% [400, 401]. Comparative studies report improvement of nail psoriasis in the same range as the above mentioned studies [377, 402, 403].

Golimumab and certolizumab pegol
Golimumab and certolizumab pegol have been registered for the treatment of PsA but not for plaque psoriasis. In randomized controlled trials these anti-TNF-α antibodies have been shown to be effective treatments for nail psoriasis in patients with PsA who often also use methotrexate, sulfasalazine, leflunomide, or oral corticosteroids [405, 413, 485].

Secukinumab
Secukinumab targets IL-17A and has been approved for the treatment of plaque psoriasis and PsA. Little is known about the efficacy of secukinumab in nail psoriasis. One subanalysis of a dose-finding randomized controlled trial reported secukinumab improvement of nail lesions in moderate to severe plaque psoriasis [429]. Unfortunately, a never before described composite score was used, and no patients received the eventually approved dose for plaque psoriasis. A randomized controlled trial investigating the efficacy at 16 weeks of secukinumab 150 and 300 mg in subjects with moderate
to severe nail psoriasis has been conducted and appears to have shown improvement, but results have not been published yet in a peer-reviewed journal.

IxEKizumab
IxEKizumab is another anti-IL-17A antibody registered for plaque psoriasis. Data on nail psoriasis are available and suggest very good efficacy [424–426, 428]. Improvement of nail psoriasis is in the same range as with other biologics. Complete clearance of the nails was achieved in 51% at week 68 in a randomized controlled trial, a high proportion of patients [425]. The UNCOVER-3 trial randomized patients to placebo, etanercept, or ixEKizumab [428]. After 60 weeks about 55% of patients on ixEKizumab experienced complete clearance of fingernail psoriasis.

Ustekinumab
Ustekinumab is an anti-IL-12/23 monoclonal antibody that is indicated for the treatment of plaque psoriasis and for PsA. Case reports and a series also suggested good efficacy in nail involvement [430, 434]. After prolonged use up to 97% improvement in nail psoriasis was reported [431, 433]. Also QoL scores significantly improved. In two randomized controlled trials, the efficacy of ustekinumab in nail psoriasis is slightly less [432, 435]. In the PHOENIX-1 study nail improvement was 57%, and was highest in patients with a good PASI response [435]. Positive effects of ustekinumab on both nail bed and nail matrix psoriasis were reported. Interestingly, it has also been shown that a smaller proportion of patients with nail psoriasis achieved PASI of 75% at 24 weeks than patients without nail psoriasis [485]. A small retrospective comparative study was unable to show differences in clinical efficacy on nail psoriasis between ustekinumab and several other anti-TNF-α treatments [400].

Nail psoriasis and psoriatic arthritis

Signs of nail psoriasis are more common in patients with PsA than in patients with psoriasis vulgaris. Nail changes were present in 51–87% of patients with PsA [234, 332, 359, 488–490]. In contrast, 29–39% of patients with nail psoriasis had PsA [212, 486, 487]. In one study, psoriatic nail changes were able to predict the onset of PsA with a risk ratio of 2.24 on multivariate analysis [491]. Asymptomatic enthesitis, as a risk factor for developing destructive PsA, had a higher prevalence in patients with nail psoriasis than in patients with psoriasis without nail involvement [491, 492]. Presence of nail psoriasis offers an opportunity for early diagnosis of PsA that may prevent subsequent joint destruction [493]. There is good evidence that all of the anti-psoriatic biologic treatments available prevent progression of this damage [235, 494]. Clinical nail changes in patients with PsA vary from mild pitting to gross destruction [489]. Lavaroni et al. [361] found great toenail subungual hyperkeratosis to be the most common finding followed by fingernail pitting. Love et al. [493] and Klaassen et al. [495] found that onycholysis was the nail change most strongly associated with small joint disease in PsA. These studies found no association between small joint arthritis and pitting, oil spots, or subungual hyperkeratosis. Diagnosis of PsA is based on the CASPAR criteria [496], which score presence of joint and skin disease, personal and family history of psoriasis, nail signs, dactylitis, radiographic signs, and the absence of rheumatoid factor. Typical PsA symptoms include pain, swelling, and morning stiffness of the affected joints. Common inflammation sites include inflammation of entheses (tendon or ligament insertions), dactylitis (swelling of a whole digit), and involvement of the axial skeleton. A number of typical patterns of peripheral joint disease have been described [496], including predominant DIP involvement, arthritis mutilans (a highly destructive arthritis with bone lysis and telescoping of the digits), a symmetrical polyarthritis similar to rheumatoid arthritis, an asymmetrical oligoarthritis, and predominant axial disease. Blood tests are more likely to be normal in PsA than in rheumatoid arthritis.

Recent imaging studies have led to the hypotheses of the pathogenesis of enthesitis inflammation resulting in concomitant joint and nail disease. Using magnetic resonance imaging scans, active arthritis of the DIP joint in PsA was found to extend beyond the joint to the collateral ligaments and the extensor tendons and cause more severe changes at the corresponding DIP joint entheseseal insertions [497]. A much greater degree of extracapsular enhancement with diffuse involvement of the nailbed was also typical of PsA, thus providing a close anatomic link between nail inflammation and joint disease. Magnetic resonance imaging studies have also shown that PsA patients with nail disease are more likely to have DIP arthritis than those with clinically normal nails [498]. The study of Tan et al. [497] also indicated that pathological development in the DIP joints is largely enthesitis based. Given these findings, McGonagle et al. [499, 500] hypothesized that the entheses are the epicenter of both nail psoriasis and PsA, and nail changes are the result of enthesitis of the extensor tendon in the same anatomic region. However, it remains strange that DIP PsA often accompanies nail bed psoriasis (onycholysis) and not nail matrix psoriasis (pitting) [495], while the entheses are close to the nail matrix and far from the nail bed [495]. A clinical correlation between disease of the DIP and disease in the adjacent nail is reported by Jones [335], but denied by others [360, 489]. The near future may show if the hypothesis that an anatomic link exists between nail psoriasis and enthesitis will survive. The association between arthritis and nail disease in the same finger can also be found in the
concept of psoriatic “nail matrix arthropathy.” This concept unites the two conditions by the fact that the nail matrix and the DIP share the same blood supply [501].

Psoriasis associated with other diseases

CHILD syndrome

CHILD syndrome is an X-linked dominant inherited syndrome caused by mutation in the NSDHL (NAD(P)H steroid dehydrogenase-like protein) gene at Xq28 [502]. It is lethal to males, and clinically characterized by a peculiar congenital homolateral inflammatory skin condition with a pronounced affinity for the body folds [503–505]. The acronym stands for congenital hemidysplasia with ichthyosiform nevus and limb defects. Cases are sporadic and familial [505].

Nail changes in CHILD syndrome have been reported as periungual hyperkeratosis with fissuring and dystrophic nail plates (Fig. 14.125) [505, 506]. Patients may have aplasia of the distal phalanx. Changes in psoriasis have been reportedly associated with unilateral...
underdeveloped long bones and central nervous system anomalies [507], but the clinical changes may more appropriately belong to the CHILD syndrome [508] or CHILD nevus [509] disease spectrum.

**Acquired immunodeficiency syndrome**

Psoriasis and reactive arthritis may be exuberant and more treatment resistant in patients with AIDS [510, 511], although psoriatic nail disease is uncommon. In one prospective study of 155 HIV-infected patients none were found to have features of nail psoriasis [512].

**Medication-induced psoriasis**

Severe exacerbation of psoriasis may be due to drugs (Box 14.1) [513–515]. Beta-blockers, lithium, and antimarials are the drugs most associated with development or exacerbation of psoriasis [513]. Pitting and onycholysis in four of 10 patients who developed psoriasis or had an exacerbation of psoriasis when placed on beta-blockers were reported by Savola et al. [516]. Psoriasis-like lesions involving the nail area can appear de novo and they can disappear after the beta-blocker is discontinued [517, 518]. Beta-blocker-induced psoriasis can also be limited to the nails without plaque psoriasis [519]. Also topical timolol eye drops can cause nail psoriasis [520]. Lithium can aggravate and/or precipitate plaque psoriasis [521] and nail disease [522] (Fig. 14.126).

**References**


Palmou N, Marzo-Ortega H, Ash Z et al. (2011). Linear pitting and splinter haemorrhages are more commonly seen in the nails of patients with established psoriasis in comparison to psoriatic arthritis. Dermatology. 223 (4): 370–373.


Rich P, Griffiths CEM, Reich K et al. (2008). Baseline nail disease in patients with moderate to


Dermatological Disorders


386 Bianchi L, Soda R, Diluvio L et al. (2003). Tazarotene 0.1% gel for psoriasis of the fingernails and toenails:


411 Ortonne JP, Paul C, Berardesca E et al. (2013). A 24-week randomized clinical trial investigating the


Dermatological Disorders


466 Nakamura RC, Abreu L de, Duque-Estrada B et al. (2012). Comparison of nail lacquer clobetasol efficacy at 0.05%, 1% and 8% in nail psoriasis treatment: prospective, controlled and randomized pilot study. *An Bras Dermatol.* 87 (2): 203–211.


491 Wilson FC, Icen M, Crowson CS et al. (2009). Incidence and clinical predictors of psoriatic arthritis


Part VII
The Nail in Systemic Conditions

Chapter 15
The Nail in Systemic Disease

Mark Holzberg¹ and Bianca Maria Piraccini²

¹ Department of Dermatology, Emory University School of Medicine, Atlanta, GA, USA
² Dermatology, Department of Experimental, Diagnostic and Specialty Medicine, University of Bologna, Bologna, Italy

<table>
<thead>
<tr>
<th>CHARTER MENU</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cardiac disorders, 482</td>
</tr>
<tr>
<td>Congenital heart disease, 482</td>
</tr>
<tr>
<td>Cardiac failure, 483</td>
</tr>
<tr>
<td>Bacterial endocarditis, 483</td>
</tr>
<tr>
<td>Embolus, 484</td>
</tr>
<tr>
<td>Circulatory disorders, 484</td>
</tr>
<tr>
<td>Ischemia and gangrene, 484</td>
</tr>
<tr>
<td>Arterial disease, 485</td>
</tr>
<tr>
<td>Thromboangiitis obliterans (Buerger disease), 485</td>
</tr>
<tr>
<td>Venous disease, 485</td>
</tr>
<tr>
<td>Acrocyanosis, 486</td>
</tr>
<tr>
<td>Cutaneous reaction to cold, 486</td>
</tr>
<tr>
<td>Raynaud phenomenon and Raynaud disease, 489</td>
</tr>
<tr>
<td>Erythromelalgia, 490</td>
</tr>
<tr>
<td>Ainhum and pseudoainhum, 490</td>
</tr>
<tr>
<td>Respiratory disorders, 490</td>
</tr>
<tr>
<td>Yellow nail syndrome, 491</td>
</tr>
<tr>
<td>High altitude, 493</td>
</tr>
<tr>
<td>Asthma and bronchitis, 493</td>
</tr>
<tr>
<td>Smoking, 493</td>
</tr>
<tr>
<td>Bronchiectasis, 494</td>
</tr>
<tr>
<td>Sarcoïdosis, 494</td>
</tr>
<tr>
<td>Lung infections, 494</td>
</tr>
<tr>
<td>Gastrointestinal disorders, 494</td>
</tr>
<tr>
<td>Celiac disease, 494</td>
</tr>
<tr>
<td>Peutz–Jeghers syndrome, 495</td>
</tr>
<tr>
<td>Plummer–Vinson syndrome, 495</td>
</tr>
<tr>
<td>Inflammatory bowel disease, 495</td>
</tr>
<tr>
<td>Cronkhite–Canada syndrome, 495</td>
</tr>
<tr>
<td>Intestinal infections, 496</td>
</tr>
<tr>
<td>Glucagonoma syndrome, 496</td>
</tr>
<tr>
<td>Hepatic disorders, 497</td>
</tr>
<tr>
<td>Cirrhosis, 497</td>
</tr>
<tr>
<td>Wilson disease, 498</td>
</tr>
<tr>
<td>Hemochromatosis, 498</td>
</tr>
<tr>
<td>Renal disorders, 498</td>
</tr>
<tr>
<td>Hypoalbuminemia, 499</td>
</tr>
<tr>
<td>Renal failure – hemodialysis, 499</td>
</tr>
<tr>
<td>Calciphylaxis, 501</td>
</tr>
<tr>
<td>Nephrotic syndrome, 501</td>
</tr>
<tr>
<td>Renal transplantation, 501</td>
</tr>
<tr>
<td>Reproductive system disorders, 502</td>
</tr>
<tr>
<td>Pregnancy, 502</td>
</tr>
<tr>
<td>Menstruation, 502</td>
</tr>
<tr>
<td>Endocrine disorders, 503</td>
</tr>
<tr>
<td>Diabetes mellitus, 503</td>
</tr>
<tr>
<td>Hypogonadism, 505</td>
</tr>
<tr>
<td>Pituitary disease, 505</td>
</tr>
<tr>
<td>Adrenal disease, 505</td>
</tr>
<tr>
<td>Parathyroid disease, 505</td>
</tr>
<tr>
<td>Thyroid disease, 507</td>
</tr>
<tr>
<td>Nervous system disorders, 507</td>
</tr>
<tr>
<td>Syringomyelia, 507</td>
</tr>
<tr>
<td>Hemiplegia, 507</td>
</tr>
<tr>
<td>Spinal cord injuries, 508</td>
</tr>
<tr>
<td>Congenital absence of pain, 508</td>
</tr>
<tr>
<td>Peripheral neuropathies, 509</td>
</tr>
<tr>
<td>Unilateral nail changes secondary to anticancer therapy neuropathies, 509</td>
</tr>
<tr>
<td>Cervical rib syndrome, 509</td>
</tr>
<tr>
<td>Carpal tunnel syndrome, 510</td>
</tr>
<tr>
<td>Peripheral nerve injuries, 510</td>
</tr>
<tr>
<td>Complex regional pain syndrome, 511</td>
</tr>
<tr>
<td>Other central nervous system disorders, 513</td>
</tr>
<tr>
<td>Polymyelitis, 513</td>
</tr>
<tr>
<td>Psychological and psychiatric disorders, 513</td>
</tr>
<tr>
<td>Onychophagia, 513</td>
</tr>
<tr>
<td>Schizophrenia, 514</td>
</tr>
<tr>
<td>Anorexia nervosa and other eating disorders, 515</td>
</tr>
<tr>
<td>Musculoskeletal disorders, 515</td>
</tr>
<tr>
<td>Osteoarthritis, 515</td>
</tr>
<tr>
<td>Still disease, 515</td>
</tr>
<tr>
<td>Chronic recurrent multifocal osteomyelitis, 516</td>
</tr>
<tr>
<td>Hematological and lymphatic disorders, 516</td>
</tr>
<tr>
<td>Anemia, 516</td>
</tr>
<tr>
<td>Polycythemia vera, 516</td>
</tr>
<tr>
<td>Thrombocytopenia, 516</td>
</tr>
<tr>
<td>Hemoglobinopathy, 516</td>
</tr>
<tr>
<td>Hereditary hemorrhagic telangiectasia (Osler–Weber–Rendu syndrome), 516</td>
</tr>
<tr>
<td>Heavy chain disease, 516</td>
</tr>
<tr>
<td>Cryoglobulinemia, 517</td>
</tr>
<tr>
<td>Plasmyctoma and multiple myeloma, 517</td>
</tr>
<tr>
<td>Castleman disease, 518</td>
</tr>
<tr>
<td>Leukemia, 518</td>
</tr>
<tr>
<td>Lymphoma, 519</td>
</tr>
<tr>
<td>Connective tissue diseases, 520</td>
</tr>
<tr>
<td>Capillaroscopy, 520</td>
</tr>
<tr>
<td>Rheumatoid arthritis, 530</td>
</tr>
<tr>
<td>Antiphospholipid antibody syndrome, 532</td>
</tr>
<tr>
<td>Antisynthetase syndrome, 532</td>
</tr>
<tr>
<td>Granulomatosis with polyangiitis (Wegener granulomatosis), 532</td>
</tr>
<tr>
<td>Periarteritis nodosa, 532</td>
</tr>
<tr>
<td>Microscopic polyarteritis, 533</td>
</tr>
<tr>
<td>Multicentric reticulohistiocytosis, 533</td>
</tr>
<tr>
<td>Follicular mucinosis (alopecia mucinosa), 534</td>
</tr>
<tr>
<td>Fibroblastic rheumatism, 534</td>
</tr>
<tr>
<td>Reiter syndrome, 534</td>
</tr>
<tr>
<td>Kawasaki disease (mucocutaneous lymph node syndrome), 534</td>
</tr>
</tbody>
</table>
Cardiac disorders

Congenital heart disease

Clubbing is a common feature of congenital cardiovascular cyanotic disease (Fig. 15.1) and the regional differential distribution of clubbing and cyanosis may give a clue to the anatomical identification of the specific abnormality [1, 2]. Congenital heart disease with right-to-left shunt results in symmetrical clubbing and cyanosis of fingers and toes. Complete transposition of the great vessels with a reversed shunt from the pulmonary artery into the aorta through a patent ductus arteriosus delivering oxygenated blood to the lower limbs results in clubbing and cyanosis more evident on fingers than on toes. The anatomical proximity of the ductus to the left subclavian artery may result in differential cyanosis of the arms as well, since oxygenated blood from the pulmonary artery may enter the left subclavian artery through the ductus. The presence of coarctation or a complete interruption of the aortic arch may make the difference between upper and lower limbs more obvious.

Cyanosis and clubbing or hypertrophic osteoarthropathy of the lower extremities can occur secondary to a patent ductus arteriosus with reversal of blood flow. The left hand can manifest minimal cyanosis when the left subclavian artery receives unsaturated blood from the patent ductus, while the right hand is normal. Hypertrophic osteoarthropathy (Fig. 15.2) is also a typical feature of Eisenmenger syndrome, the most severe form of pulmonary arterial hypertension that arises on the basis of congenital heart disease with a systemic-to-pulmonary shunt.

Quincke’s pulse is a physical finding of severe and chronic aortic insufficiency. It results from a capillary
pulse in the nail bed or nail fold synchronized with the heart and appears as an alternating flushing and blanching of the nail bed of the fingers [3]. The prominence of the proximal nail fold capillary loops is an associated distinctive sign.

Splinter hemorrhages have been reported to involve the whole nail bed in patients with cyanotic congenital heart disease and in congenital arteriovenous fistula of the lung [4].

Red fingertips can be a sign of small or intermittent right-to-left shunts, which cause a minimal reduction of the arterial oxygen saturation (tuft erythema).

**Cardiac failure**

Red lunulae are characterized by intense redness of the proximal lunula that fades distally and disappears with pressure on the proximal nail plate. A narrow white band may be present at the distal limit with the pink nail bed [5, 6]. Red lunulae mainly involve the thumbs, where the lunulae are usually clearly visible, and have been described in association with many disease states (see Appendix).

In cardiac disease, red lunulae have been associated with congestive heart failure, coronary thrombosis, coronary atherosclerotic disease, angina pectoris, conduction abnormalities, hypertension, myocardial infarction, and rheumatic heart disease [6–8].

Possible pathogenesis of red lunulae includes an increase in arteriolar blood flow, a vasodilatory capacitance phenomenon, or changes in the optical properties of the overlying nail plate so that normal vessels become more apparent [8, 9].

Terry’s nails, a variety of apparent leukonychia that involves the proximal nail fading the lunula with a 0.5–3.0 mm transverse red to brownish band on the distal nail edge, can be observed in chronic congestive heart failure, especially in younger patients [10].

The yellow nail syndrome has been associated with myocardial infarction [11] and with pericarditis and pericardial effusion [12].

A complete form of pachydermoperiostosis, hyperostosis, finger clubbing, and pachydermia (hypertrophic osteoarthropathy) has been described in a 34-year-old patient with heart failure [13].

**Bacterial endocarditis**

Finger clubbing is reported to occur in 7–52% of patients with bacterial endocarditis and is usually a late sign [14]. A patient with bacterial endocarditis associated with clubbing experienced complete regression of the nail signs after surgical replacement of mitral and aortic valves [15].

Osler’s nodes and Janeway lesions are important clinical clues for the diagnosis of subacute bacterial endocarditis. Osler’s nodes are small red tender nodules localized in the finger pulp and in the proximal and lateral nail folds (Fig. 15.3). They develop over a period of hours to days. Janeway lesions are non-tender hemorrhagic or nodular lesions localized on the palms and soles [13, 14, 16, 17]. Both types of lesions result from septic microemboli and are pathologically characterized by neutrophilic dermal abscesses with clumps of gram-positive bacteria in dermal vessels [18–20].

Acral cyanosis evolving towards purpura and even necrosis has been reported during widespread intravascular coagulation complicating acute bacterial endocarditis (Fig. 15.4) [21].

![Figure 15.3 Osler’s nodes: hemorrhagic tender nodules around the nail suggestive of bacterial endocarditis.](image1)

![Figure 15.4 Acral cyanosis associated with disseminated intravascular coagulation. Courtesy of C.I. Beylot.](image2)
In subacute bacterial endocarditis, splinter hemorrhages result from septic and non-septic emboli in the terminal vessels of the nail bed. They are often painful and are typically localized both proximally and distally within the nail [21].

**Emboli**

Splinter hemorrhages resulting from emboli in the terminal vessels of the nail bed can be observed in patients with an arterial embolus or with mitral stenosis or from cholesterol emboli [22].

**Circulatory disorders**

**Ischemia and gangrene**

Early in peripheral arterial disease, the vascular supply to the digit decreases with changes evident in the nail apparatus. A decrease in the blood supply in the nail matrix leads to production of thin and brittle nail plates with onychorrhexis and distal breakage and splitting. Severe thinning may lead to koilonychia. Impaired nail bed vascularization results in onycholyis and apparent leukonychia. If the vascular changes are intermittent, the nail plate shows transverse depressions (Beau’s lines), each indicating a single episode of ischemia, but if the decreased vascular supply is persistent, a complete shedding of the nail plate (onychomadesis) can occur.

Hand surgeons have noticed Beau’s lines secondary to ischemia following the use of an upper extremity tourniquet [23].

Acute digital ischemia (blue digit syndrome) may have a variety of causes and requires immediate treatment in order to prevent limb gangrene [24, 25]. The digit becomes blue and this blue color is reflected in the nail bed as a dusky color change of the lunula. Acute coronary ischemia can cause ischemia affecting a single hand, especially the left, and should suggest a diagnosis of shoulder–hand syndrome due to reflex vasospasm. Loss of demarcation of the margin of the lunula (pseudomaculunulae) can be a sign of hand ischemia.

Cholesterol embolism is a multisystemic disorder with a poor prognosis that may develop spontaneously or follow a vascular procedure and originates from the breakdown of atherosclerotic plaques in the aortic wall. Renal failure and cutaneous lesions, including blue toe syndrome, livedo reticularis, ulceration, or gangrene, are two of the most common clinical manifestations [26]. In blue toes, which are most evident when the patient is upright, the affected toes are blue, cyanotic, painful, and cool to touch. Peripheral pulses are often preserved. The lesion might progress to ulceration, digital infarcts, or gangrene needing amputation. A case of cholesterol embolization resulting in painful purple-erythematous macules and livedo on the fingers and dorsum of the left hand has been reported in an 85-year-old Japanese man [27]. The diagnosis is histopathologically established by documenting occlusion of arterioles with atheromatous debris containing cholesterol crystals. Cholesterol microembolization has also been associated with punctiform subungual hemorrhages of the fingers [28, 29].

Chronic digital ischemia of the lower limbs causes the nail plate to become distorted, thickened, rough, and darkened. Nail growth is often reduced and onychogryphosis may occur. Periungual hyperesthesia, which can accompany severe digital ischemia, should be differentiated from an ingrown toenail. Improvement of the circulation is usually followed by nearly normal growth of the nail plate.

Unilateral digital ischemia may result from repetitive use of the hypothenar eminence as a hammer, which results in damage and thrombus formation in the ulnar artery and superficial palmar arch. The hypothenar hammer syndrome occurs mainly in men with a mean age of 40 years and involves the second, third, fourth, and fifth digits of the dominant hand [30]. It is usually occupational: workers most at risk include metal workers, auto mechanics, lathe operators, machinists, miners, sawmill workers, butchers, bakers, brick layers, and carpenters [31].

Volkmann syndrome (Volkmann contracture, Volkmann ischemic contracture) is a permanent flexion contracture of the hand at the wrist due to shortening of forearm muscles, which gives rise to a claw-like deformity of the hand, fingers, and wrist. It is caused by obstruction of the brachial artery near the elbow and occurs in children or adults who have suffered intense trauma, prolonged external compression, excessive exercise, burns, or animal bites [32]. A rare neonatal variety has also been reported [33, 34]. On examination, the fingers are white or blue and cold and the radial pulse is absent. The fingers become thinned and tapered and the nail may become overcurved.

Digital ischemia may present as a paraneoplastic condition, with a prevalence of paraneoplastic acral vascular syndromes ranging from 2.2% to 8% of cases [35]. It has been associated mainly with adenocarcinoma of the lung, ovary, or digestive tract, hematological malignancies, and epidermoid or anaplastic carcinomas [36]. Ischemia may progress to gangrene (Fig. 15.5) and in the majority of patients it occurs simultaneously with the cancer. It has an evolution closely linked to that of the tumor. The pathogenesis of digital ischemia associated with malignancy is probably multifactorial. Possible mechanisms include metastatic involvement of the sympathetic ganglia, production of vasoconstrictive substances by the tumor, thromboemboli by fragments of the tumors, and immunological factors.
Digital ischemia due to peripheral vasoconstriction caused by crack cocaine use can induce hand and fingernail changes in long-term consumers, especially females. The hands are cold and numb, sometimes with hyperkeratosis over the knuckles, with finger pulp atrophy of some digits, especially the thumb and index finger, resulting in claw-like curvature of the nails (parrot-beak nails) [37].

Arterial disease

Hypertrophic osteoarthropathy of the lower limbs can be the initial sign of an aortic graft infection [38, 39]. Patients usually suffer from progressive pain and swelling of one or both extremities, associated with radiographic periostosis. The additional finding of Osler’s nodes is another useful clue for the diagnosis of arterial graft sepsis.

Thromboangiitis obliterans (Buerger disease)

Thromboangiitis obliterans or Buerger disease is a rare form of vasculitis that affects the small and medium-sized arteries and veins of the limbs, typically occurs in young, mostly male, subjects, and is strongly associated with tobacco smoking [40]. Obstruction of large arteries can result in digital ischemia and gangrene. In the early phases, painful vesicles develop in the digit pulp with intense hyperemia, hypersensitivity of the surrounding skin, and a pseudowhitlow presentation. Subungual splinter hemorrhages have been reported as another early symptom [41]. Late in Buerger disease, ulceration and gangrene develop at the sides of the nails or the tips of the digits, especially after trauma (Figs 15.6, 15.7). Growth abnormalities of the nails are common [42].

Venous disease

Ischemic venous thrombosis is a peripheral tissue ischemia caused by extensive deep venous thrombosis, which usually involves the lower limbs. Predisposing factors include pregnancy, immobility, and coagulation disorders. When ischemic venous thrombosis involves the foot, the digits develop gangrene, initially presenting as a livid discoloration of the involved skin with petechiae, purpura, and bullae, and finally as a sharply demarcated necrotic black area [43].

In chronic venous insufficiency of the legs, the toenails become thickened and darker in color (Fig. 15.8). Onychomycosis due to dermatophytes and non-dermatophytes is very frequent affecting 60–84% of the
patients [44, 45] and difficult to cure, with advanced patient age and long duration of vein disease as poor prognostic factors [44].

Clubbing has been described in heroin addiction and has been attributed to chronic obstructive phlebitis of the arm veins due to repeated intravenous heroin injections [46].

**Acrocyanosis**

Acrocyanosis is characterized by persistent abnormally deep blue or cyanotic discoloration of the skin over extremities (hands and feet most commonly) due to decreased oxyhemoglobin within the vessels of the dermis and hypodermis.

In acrocyanosis, asymptomatic persistent violaceous dusky discoloration symmetrically involves the hands and less frequently the feet [47]. The nail bed is cyanotic and chronic paronychia can be observed. Other possible nail changes include brittleness, trachyonychia, splinter hemorrhages, Beau's lines, onycholysis, and subungual hyperkeratosis (Fig. 15.9).

Nail fold capillaroscopy may help in differential diagnosis between acrocyanosis and connective tissue disorders, mainly Raynaud phenomenon, although changes of the nail fold capillaries are detectable in only 75% of patients [48]. Capillaroscopy in acrocyanosis shows hemorrhages, pericapillary edema, widened capillaries, and often thrombosis, with reduced capillary density (Figs 15.10, 15.11).

**Cutaneous reaction to cold**

When the skin is exposed to freezing temperatures, there is initially vasoconstriction as the cooled blood slows down reflexes to conserve heat. The reduced blood flow to the skin conserves heat in the body, but leaves the skin more vulnerable to the cold. When the skin temperature
drops to about 15°C, it suddenly reddens as the low skin metabolism induced by vasoconstriction induces a relative oxygen surplus in the tissues. As the skin temperature falls below 0°C, it freezes solid with a white waxy pallor and anesthesia and diffuse tissue damage typical of frostbite.

Exposure to cold temperatures can damage the nail matrix, leading to Beau’s lines and onychomadesis. Severe cold exposure not amounting to frostbite may be associated with acroosteolysis resulting in brachyonychia [49]. In severe frostbite, gangrene of the fingertips and toes may lead to amputation (Fig. 15.12) or to brachyonychia due to latent bone destruction [50]. A case of hemorrhages of the distal proximal nail fold after cold injury has been described in a mountaineer after frostbite [51].

Perniosis, also called pernio or chillblain, represents an abnormal vascular response to cold exposure which occurs most frequently in women, children, and elderly people. In acute perniosis, the lesions are usually bilateral, symmetrical, and self-limiting and appear as tender erythematous plaques (Figs 15.13–15.15). In more severe cases, vesicles, bullae, petechiae, hemorrhages, and ulcers can occur. In chronic perniosis, the lesions begin as burning erythematous blue patches that develop into tender nodules and then into hemorrhagic bullae that rupture, leaving shallow, slow-to-heal ulcers. Nail changes that have been associated with recurrent
perniosis include longitudinal ridges [52] and postinflammatory melanonychia associated with periungual hyperpigmentation [53]. Beau’s lines and subungual hemorrhages may follow perniosis of the proximal nail fold (Fig. 15.16). Nail fold capillaroscopy of pernio shows increased capillary diameter and increased apical capillary diameter independent of disease activity [54].

**Figure 15.12** Gangrene due to frostbite. Courtesy of G. Webster.

**Figure 15.13** Perniosis: erythemat-violaceous paronychia after exposure to cold.

**Figure 15.14** Perniosis: erythemat-violaceous plaque on the distal digit.

**Figure 15.15** Chilblains (perniosis).

**Figure 15.16** Beau’s lines and subungual hemorrhages after perniosis with lesions on the proximal nail fold.
The Nail in Systemic Disease

Raynaud phenomenon and Raynaud disease

Primary Raynaud phenomenon is recurrent vasospasm of the fingers and toes that usually occurs in response to stress or cold exposure not associated with other illnesses. In Raynaud disease, on the other hand, Raynaud phenomenon (secondary Raynaud phenomenon) is associated with other conditions, mainly autoimmune disorders, the most common being systemic sclerosis. Key investigations to distinguish the two conditions are nail fold capillaroscopy and testing for autoantibodies. In Raynaud phenomenon, the classic triphasic color changes characterized by “white finger syndrome” are due to acute vasoconstriction followed by cyanosis and finally hyperemia (Fig. 15.17). Bilateral symmetrical involvement of multiple digits is usually observed. Permanent cyanosis occurs in advanced cases. Nail changes observed in Raynaud phenomenon possibly derive from repeated episodes of transitory ischemia and include thinning, koilonychia, brittleness, and distal splitting. Nail plate thickening and transverse leukonychia can also occur. Recurrent bouts of vasospasm can lead to Beau’s lines. A case of yellow nail syndrome associated with arterial insufficiency and Raynaud disease has been reported [55]. Splinter hemorrhages have been associated with Raynaud disease [56] and the rapid onset of Raynaud phenomenon associated with digital ulcers and multiple splinter hemorrhages has been reported as a sign of metastatic breast cancer in a woman considered free of disease [57].

Massive digital necrosis resulting from severe Raynaud phenomenon can also be the first manifestation of a collagen vascular disease [58], as digital gangrene is not usually associated with primary Raynaud phenomenon. The most useful signs for predicting the development of a collagen vascular disease in patients with Raynaud phenomenon are pitting scars of the digit pulp, puffy fingers, the presence of antinuclear antibodies, and capillaroscopy changes [59].

The altered vasospastic reaction that characterizes patients with primary Raynaud phenomenon is a risk factor for development of digital gangrene in particular instances, such as injection of epinephrine with anesthetic during surgical procedures to the finger [60, 61].

Over time, chronic paronychia, dorsal or ventral pterygium, acroosteolysis, painful puckered ulcers of the fingertips and, rarely, gangrene develop as signs and symptoms of severe Raynaud disease, just as in chronic ischemia (Figs 15.18–15.20). Physical examination, screening for antinuclear antibodies, capillaroscopy, and radiography of the hands and chest are useful in distinguishing Raynaud disease from the early stage of systemic scleroderma. Asymmetrical involvement of a...
few digits suggests Raynaud phenomenon secondary to arterial diseases. Other possible causes of Raynaud phenomenon include drugs, occupation, hematological diseases, hepatitis B infection, neurovascular compression, and tumors [62].

**Erythromelalgia**

Erythromelalgia is characterized by burning pain in the extremities associated with local erythema and warmth and is usually aggravated by exercise or warming. It may be idiopathic or secondary to other conditions, most commonly myeloproliferative disorders. Apparent leukonychia with proximal white nail and normal distal border have been described in one case of primary erythromelalgia [63]. Acrocyanosis and gangrene of the digits can occasionally occur.

**Ainhum and pseudoainhum**

Ainhum presents as a painful constricting band that encircles the fifth toe with eventual spontaneous amputation. It may be unilateral but 75% of cases are bilateral. It typically affects the black population of subtropical regions of America, Africa, and Asia. The condition is often secondary to an abnormality in the foot vessels producing an abnormal blood supply alone or in combination with chronic trauma and infection [64].

Similar changes occur in pseudoainhum caused by constriction by external forces, such as hair or threads, encountered in children or mentally deranged adults (Fig. 15.21). Removal of the constricting band and performance of a Z-plasty may prevent spontaneous amputation.

**Respiratory disorders**

Clubbing has been observed in a variety of respiratory illnesses including pulmonary abscesses and cysts, pulmonary endarteritis, pulmonary fibrosis and chronic passive congestion, and mediastinal tumors such as fibrosarcoma. It has been associated with respiratory carcinomas and with cystic fibrosis, asbestosis, hypersensitivity pneumonitis, pulmonary arteriovenous malformation, hepatopulmonary syndrome, and sarcoid [65].
Yellow nail syndrome

The yellow nail syndrome (YNS) is an uncommon disorder of unknown etiology characterized by the triad of yellow nails, lymphedema, and respiratory tract involvement. However, these three features are simultaneously present in only one-third of the cases and the presence of typical nail alterations is an absolute requirement for the diagnosis. Other respiratory conditions such as cough, bronchitis, tracheobronchitis, bronchiectasis, chronic sinusitis, chronic respiratory infections, and pleural effusions have been associated with the nail changes.

The pathogenesis of the nail and systemic manifestations of yellow nail syndrome is unresolved. Impaired lymphatic drainage appears to play a central role in the various clinical findings seen. Lymphangiograms generally have shown abnormal findings such as atresia, hypoplasia, and varicose abnormalities of peripheral lymphatics, but this has not been a consistent finding. Results of quantitative lymphoscintigraphy of 17 subjects with yellow nail syndrome suggest that the lymphatic impairment is not due to anatomical abnormalities, but rather to a functional disorder. This hypothesis is confirmed by reversibility of lymphedema in this condition [66]. Several other possible pathogeneses have been suggested to explain the occurrence of yellow nail syndrome, including titanium exposure [67, 68], but this hypothesis is far from being reliable [69].

Nail changes in yellow nail syndrome are pathognomonic. Both fingernails and toenails are affected (Fig. 15.22). Nail signs diagnostic for yellow nail syndrome are arrested or slowed nail growth rate, nail plate thickening, lack of cuticles, yellow-green discoloration, and increased transverse curvature of the nail plate (Figs 15.23–15.26). The cuticles are absent and the proximal nail folds are swollen, the nail plate is thickened, hard, and opaque, and increased transverse curvature leads to onycholysis with possible shedding of the nail. The clinical appearance of the nail is most probably dependent on the extremely slow growth rate [70]. Patients often remark that their nails have stopped growing. Nail growth is approximately 50% that of normal nails (0.23 mm/week compared to 0.46 mm/week in normal nails) and the nail plate is twice as thick. The resolution of the nail changes is, in fact, always associated with resumption of normal nail growth.

Histologically, typically there are no changes in the nail plates of patients with yellow nail syndrome. In some

Figure 15.22 Yellow nail syndrome involving both fingernails and toenails.

Figure 15.23 Yellow nail syndrome: absence of the cuticle, yellow nail discoloration, and increased transverse curvature.
Figure 15.24 Yellow nail syndrome: absence of the cuticle, yellow nail discoloration and increased transverse curvature leading to onycholysis involves fingernails and toenails.

Figure 15.25 Yellow nail syndrome: several nail plates have been shed due to extensive onycholysis.

Figure 15.26 Yellow nail syndrome: nail changes associated with lymphedema.
patients, nail histology is normal; there are no demonstrable changes in small vessels and dermal lymphatic function is normal [71]. In others, histopathology of the nail matrix and bed demonstrates dense, fibrous tissue replacing subungual stroma with numerous ectatic, endothelium-lined vessels that are similar to the histology in the pleura in yellow nail syndrome [72]. Sclerosis of the subungual tissue is postulated to lead to lymphatic obstruction. On electron microscopy, keratohyalin granules are seen in the nail matrix and have been postulated to be associated with slow nail growth [73].

Epidemiologically, yellow nail syndrome is more common in adults [74] but it can rarely occur in children [75, 76] and be congenital [76–79]. Males and females are equally affected. While the syndrome was initially classified as hereditary with familial cases reported [76, 80, 81], contemporary literature recognizes a predominance of acquired cases [82].

Nail changes may precede the development of lymphedema or respiratory manifestations by years. When it occurs, lymphedema usually begins in the ankles and legs but the hands or even the face can be affected. It can rarely be generalized. Congenital lymphedema has also been reported in association with yellow nail syndrome. Possible association of yellow nail syndrome with intestinal lymphangiectasia has rarely been reported [83, 84].

Respiratory manifestations of yellow nail syndrome include chronic inflammatory/infective disorders, such as asthma, chronic sinusitis [85, 86], bronchiectasis [87], chronic bronchitis, pulmonary fibrosis, giant cell interstitial pneumonitis, pneumonia, tuberculosis, chylothorax, and thoracic tumors including thoracic non-malignant lymphatic disorders [88] and lung cancer [89, 90]. Removal of the tumor may or may not be associated with improvement of the nail signs.

Other non-respiratory associations, usually reported in single case reports, can be found in the Appendix and in the respective sections within this chapter.

Improvement or spontaneous resolution of nail changes associated with improvement of the systemic manifestations of yellow nail syndrome has been reported in up to 30% of the cases [74]. Various therapeutic regimes for the nail changes have been reported, but none have shown consistent results. Oral α-tocopherol (vitamin E) at high doses, 600 to 1200 international units (IU) daily, is the only treatment that has been utilized in a large number of patients despite mixed results [74, 82, 91–93] even though it has been reported to clear the respiratory manifestations of the syndrome. Topical vitamin E solution in dimethyl sulfoxide (DMSO) has been successful in the treatment of nail changes in yellow nail syndrome in one study [94] and unsuccessful in another study [95]. Although the mechanism of action of vitamin E in yellow nail syndrome is not known, the antioxidant properties of α-tocopherol may account for its efficacy. Vitamin E has been postulated to restore the lymphatics to normal function. Pulse therapy with itraconazole 400 mg per day for 1 week a month for 6 months, with or without vitamin E, is an alternative therapy, although the real benefit of this azole, whose mechanism of action in yellow nail syndrome is thought to be stimulation of nail growth, is yet to be proven [74, 96]. Combination treatment of oral fluconazole pulse therapy and oral vitamin E is another possible option and is often cited as the best treatment of yellow nail syndrome [97].

Patients with yellow nail syndrome have several comorbidities other than the respiratory ones, possibly due to their greater age, and they generally have a lower life expectancy when compared to the normal population [98].

**High altitude**

The hypoxia associated with the hypobaric environment of high altitudes may impair normal matrix function in individuals who spend several days in this environment. Possible sequelae include Beau’s lines of several or all nails, reported in 33% of individuals who spent time at an elevation of 5000 m. The nail transverse depressions become evident after 6–8 weeks [99].

The name “Everest nails” was coined in 1997 to describe the development of bands of transverse true leukonychia in all 20 nails of a man who spent 6 weeks at extremely high altitude [100]. The length of the bands (4 mm) corresponded to the time spent in altitude-related hypoxia and was assigned to impaired nail matrix keratinization which moved distally with nail growth.

Persons spending time at high altitudes can experience splinter hemorrhages involving the distal or the whole nail bed [101–103]. Low barometric pressure may be the cause as capillary fragility increases in proportion to altitude [104].

**Asthma and bronchitis**

Minimal digital clubbing may rarely occur in children with uncomplicated asthma [105]. More severe clubbing has been reported in children with severe asthma and atopic dermatitis requiring long-term corticosteroid therapy. Clubbing completely resolved following improvement of the asthma [106].

**Smoking**

A superficial yellow-brown staining of the nail plate can be seen in smokers, most commonly on the thumb, index finger, and third fingernail of the smoker’s cigarette-holding hand [107]. The superficial nature of the staining can be easily appreciated by scraping the surface of the
nail plate with a no. 15 scalpel blade, removing the superficial discoloration. This yellow-brown pigmentation of the nail plate is referred to as “nicotine nails.” If the smoker stops, the development of a distinct line of demarcation between the distal pigmented nail and the newly emerging proximal non-pigmented nail can be appreciated. The resulting nail plate has a striped or banded appearance termed “harlequin nail” or “quitter’s nail” [108, 109].

**Bronchiectasis**

Shell nail syndrome was first described by Cornelius and Shelley [110] to describe an unusual nail deformity characterized by excessive longitudinal curvature of the nail plate associated with atrophy of the distal nail bed that involved all fingernails and the great toenails of a 37-year-old woman affected by bronchiectasis. This nail change created a small shell-like space between the curved thickened nail plate and the distal atrophic nail bed. Radiographic findings showed thinning of the distal phalanges with complete loss of tufting.

**Sarcoidosis**

Nail involvement in sarcoidosis is rare, but is clinically relevant as it indicates chronic systemic disease and is almost always associated with bone involvement in the underlying phalanges, evident as osteolysis with a lacy pattern and bone cysts on radiography [111–115]. Nail changes in the absence of bone lesions have, however, been reported [116, 117], as has nail sarcoidosis without any evidence of systemic involvement [118].

Nail abnormalities in sarcoidosis result from the presence of sarcoidal granulomas in the dermis of the different constituents of the nail apparatus [112, 119]. Type and severity of nail dystrophies depend on the localization and size of the granulomas [111–129]. Matrix compression/impaired function results in longitudinal ridging, trachyonychia, onychorrhexis, brittleness, pitting, nail atrophy, and even pterygium [125]. Nail bed changes include onycholysis, subungual hyperkeratosis, splinter hemorrhages, and red or brown discoloration.

Nail dystrophy may be associated with erythematous plaques of the proximal nail fold (paronychia) or hypochromy due to sarcoidosis of the skin adjacent to the nail and with lupus pernio. Sarcoid dactyilitis can also accompany nail sarcoidosis. It involves single or multiple digits and presents with sausage-shaped painful finger swelling [129, 130]. A necrotizing variety of sarcoid dactyilitis characterized by finger ulcerations and dystrophic nails has also been reported [131].

Nail lesions due to sarcoidosis respond to systemic treatment with oral corticosteroid and/or hydroxychloroquine. Topical clobetasol in occlusion on the affected nails can be an option when sarcoidosis of the nails is not associated with involvement of other organs [116, 128].

Finger clubbing, painful or not, is rarely associated with pulmonary sarcoidosis [132, 133], where it is considered a poor prognostic factor [134]. Hypertrophic osteoarthropathy may also be observed.

An acquired bulbous deformity of a few fingers, resembling clubbing, associated with longitudinal fissures of the nails has been described as a manifestation of sarcoid bone disease [135].

**Lung infections**

Nail changes seen in acute or chronic lung infections are rare and non-specific and result from acute systemic illness or from hypoxemia. Nail changes reported in pneumonia range from mild and transient Beau’s lines to clubbing and hypertrophic pulmonary osteoarthropathy. Hypertrophic pulmonary osteoarthropathy (Bamberger–Pierre–Marie syndrome) can also be observed in patients with chronic intrathoracic supplicative diseases such as bronchiectasis, empyema, lung abscesses, pulmonary blastomycosis, pulmonary aspergillosis, and pulmonary tuberculosis.

Finger clubbing has been found in about 30% of South African patients with tuberculosis, and leukonychia is seen in a similar percentage [136].

Red lunulae have been reported in tuberculosis and pneumonia.

Splinter hemorrhages associated with skin rash have been reported in a patient with pneumonia, respiratory failure, and disseminated intravascular coagulation caused by *Chlamydia psittaci* (psittacosis) [137].

**Gastrointestinal disorders**

Finger clubbing or hypertrophic osteoarthropathy can be seen in several gastrointestinal disorders, including inflammatory bowel diseases (ulcerative colitis, Crohn’s disease), multiple polyposis, duodenal ulcer with pyloric stenosis, and laxative abuse. Finger clubbing can be seen in patients with kwashiorkor and may be related to diarrhea.

**Celiac disease**

Acquired generalized clubbing was seen in 15% of children with celiac disease in a series of 55 cases and was considered indicative of malnutrition [138]. Nail changes are reported in 10–20% of children with celiac disease and include manifestations of iron or zinc deficiencies, such as brittle nails and koilonychia, and other symptoms, for example leukonychia, for which the pathogenesis is more difficult to explain.
Peutz–Jeghers syndrome

Peutz–Jeghers syndrome (PJS) is a rare inherited autosomal dominant disease characterized by mucocutaneous pigmentation and multiple hamartomatous polyps in the gastrointestinal tract. Brown-blue macules are seen in about 90% of the patients. They appear during the first decade of life, then fade during adolescence and mainly involve the border of the lips and oral and bowel mucosa, as well as the palms and soles (Fig. 15.27), eyes, nares, and perianal region. The pigmentation may rarely involve the nails with bands of longitudinal melanonychia of fingernails and toenails. This syndrome is important to recognize because of the increased risk for intestinal and extraintestinal malignancies. Identification of a heterozygous pathogenic variant in STK11 by molecular genetic testing confirms the diagnosis and allows for family studies.

Differential diagnosis includes Laugier and Hunziker (Laugier–Hunziker–Baran) syndrome, characterized by lenticular hyperpigmentation of the oral mucosa and longitudinal melanonychia without systemic signs or symptoms, acquired in early to mid adult life, with no evidence of a genetic transmission [139].

Plummer–Vinson syndrome

Plummer–Vinson (Plummer–Vinson–Kelly, Paterson–Brown Kelly) syndrome is a rare syndrome that presents as a classic triad of dysphagia, iron-deficiency anemia, and esophageal webs [140]. The most important possible etiological factor is iron deficiency and the resulting hypochromic anemia. Koilonychia (spoon-shaped nails) and platynychia (flat nails) occur in about half the patients and usually involve the fingernails but spare the toenails. Brittle nails are also frequently seen (Fig. 15.28).

Cronkhite–Canada syndrome

Cronkhite–Canada syndrome is a rare, acquired syndrome of unknown etiology that affects middle-aged to elderly adults and is characterized by non-familial gastrointestinal polyposis associated with diarrhea, hypoproteinemia, and weight loss. Skin hyperpigmentation and patchy or diffuse hair loss are common and nail changes are reported in 98% of patients [143]. The typical nail change is a proximal thin and soft triangular nail, white to yellow to brown-black in color, bordered by a thick and ridged nail plate (Fig. 15.30). Onycholysis, koilonychia, and recurrent onychomadesis have also been reported [144–146] (Fig. 15.31). Partial or total regeneration of the nails may occur spontaneously, in spite of active disease, or during remission.
Intestinal infections

Finger clubbing has been described in chronic bacillary dysentery, amebic dysentery, tuberculosis, ascariasis, and whipworm infestation [147]. Regression of clubbing has been reported after the eradication of ascariasis or whipworm infection.

Transverse leukonychia involving all 20 digits appeared in a patient with multiple intestinal parasitic infections [148].

Beau’s lines have been described in patients with typhoid fever.

Glucagonoma syndrome

Glucagonoma syndrome is a rare paraneoplastic phenomenon due to the presence of a glucagon-producing alpha-cell tumor of the pancreas. Necrolytic migratory
erythema is the presenting manifestation in the majority of cases. Nail changes are characteristic with chronic paronychia presenting as erythema and swelling of the proximal nail folds [149, 150] that may be associated with pyogenic granulomas [151]. Other nail abnormalities include onycholysis and nail brittleness, which in one patient recurred with recurrence of the tumor [152].

**Hepatic disorders**

Nail changes were seen in 68% of patients with liver disease (hepatitis due to hepatitis C virus [HCV] or hepatitis B virus [HBV] and hepatic failure) compared to controls [153]. Onychomycosis was the most common finding, but was considered mainly related to the work activity and the old age of these patients. Other nail changes included longitudinal striations and nail fragility, whose exact relation to liver disease was not clear, and fingernail clubbing, seen only in patients with liver failure.

Clubbing with periostitis was reported in 24% of patients with primary biliary cirrhosis, 29% of patients with HBsAg-negative chronic active hepatitis, and 23% of patients with other liver diseases in a study of 74 patients with primary biliary cirrhosis and 54 patients with other forms of chronic liver disease [154]. In the hepatopulmonary syndrome associated with liver cirrhosis, clubbing is typically associated with cyanosis. Digital clubbing associated with signs of hypoxemia was observed in the presentation of end-stage autoimmune disease complicated by hepatopulmonary syndrome in a 9-year-old child [155]. Clubbing in cirrhotics associated with hypoxemia and intrapulmonary arteriovenous shunt may resolve after transplantation.

In alcoholics, clubbing appears to be an important clue for the diagnosis of asymptomatic alcoholic hepatitis, especially when seen in patients with hepatomegaly and abnormal liver function tests [156]. Alam et al. [157] reported two patients who developed finger clubbing associated with their treatment with subcutaneous interferon-α 2A for chronic HCV infection.

Hypertrophic osteoarthropathy, with or without associated pain, can be seen in several types of chronic liver disease including primary biliary cirrhosis, bile duct carcinoma, benign bile duct stricture, chronic active hepatitis, posthepatic cirrhosis, and alcoholic cirrhosis. Clinical jaundice is present in 90% of the patients at the time of diagnosis and clubbing is present in 95% of patients [158]. Bone involvement is usually at the distal tibia and fibula and may improve after liver transplantation.

Periungual erythema and telangiectasia (red finger syndrome) have been associated with several types of hepatitis virus infection, in both HIV-positive and HIV-negative patients [159]. Another nail color change rarely associated with hepatic disorders is yellow discoloration of the nail bed in jaundice and longitudinal melanonychia, which has been reported in patients with hyperbilirubinemia. Splinter hemorrhages can be seen in patients with hepatitis.

**Cirrhosis**

Nail clippings from patients with liver cirrhosis contain an increased sodium, magnesium, and phosphorus content and a decreased sulfur and chloride content [160].

Nail changes that have been occasionally reported in patients with cirrhosis include red lunulae, splinter hemorrhages, and flat fingernails, i.e. nails that lose their curvature and become flat.

**Terry's nail**

Terry's nail is a variety of apparent leukonychia first described by Terry in 1954 in 82% of 100 cirrhotic patients [161]. In 1984, Holzberg and Walker redefined the criteria for diagnosing Terry's nail as: (i) distal thin pink to brown transverse band, 0.5–3.0 mm in width (Fig. 15.32); (ii) decreased venous return does not obscure the distal band; (iii) white or light pink proximal nail; (iv) lunula may or may not be present; (v) at least

![Figure 15.32](image-url) Terry's nails in a patient with acute myelogenous leukemia: (a) apparent leukonychia associated with absent lunula and thin distal brown transverse band, (b) histopathology of distal nail bed telangiectasias and of (c) proximal paucity of nail bed blood vessels.
four of 10 nails with the above criteria [162]. In most patients the distal pink band, which Terry termed the "onychodermal band" [163], is even, but in about one-third of the patients it is irregular (Fig. 15.33). Terry’s nails are usually bilateral and symmetrical and marked on the thumb and forefinger.

Terry associated the nail change with cirrhosis but also noted that it might be associated with other disorders. Holzberg and Walker confirmed a statistically significant association with cirrhosis, chronic congestive heart failure, and adult-onset diabetes mellitus, but Terry’s nails can also be observed in a variety of other diseases (see Appendix) and may be occasionally seen as an isolated nail finding without an associated disease. Observation of this nail color change, however, should alert the clinician to the possibility of an underlying systemic disease, especially advanced liver disease.

The pathogenesis of the white nail bed discoloration observed in Terry’s nail remains unexplained. The pathological findings of three patients who underwent longitudinal nail biopsies showed the presence of telangiectasias in the upper dermis of the distal band (Fig. 15.32) [162] suggesting that changes in nail bed vascularity may be the cause of the altered nail color.

Differential diagnosis of Terry’s nails includes other causes of apparent leukonychia such as half-and-half (Lindsay’s) nails which are typically seen in chronic renal diseases and where the distal red to brown band is wider (20–60%) than in Terry’s nails. Another condition that might be confused with Terry’s nail is Neapolitan nails, described by Horan et al. in 19% of 258 elderly patients aged more than 70 years [164]. Neapolitan nails are characterized by a loss of the lunula and three transverse bands: a proximal one of apparent leukonychia, a normal-appearing pink band in the mid nail, and an opaque band at the distal nail margin. Both Neapolitan nails and Terry’s nails may be signs of aging in people without altered liver or kidney function [165, 166].

Wilson disease

Wilson disease (hepatolenticular degeneration; WD) is a monogenic, autosomal recessively inherited condition characterized by mutations of the gene ATP7B which encodes a copper-transporting protein. Abnormal copper metabolism leads to copper accumulation primarily within the liver and subsequently in the neurological system and other tissues. The nail plates of patients with Wilson disease can harbor an increased copper content [160].

Nail changes have been reported in 24.3% of 37 children with Wilson disease and include leukonychia, onychodystrophy, pitting, and clubbing [167].

Bluish discoloration of the lunulae (blue lunulae, azure lunulae) is the most striking nail change seen in patients with Wilson disease, being reported in approximately 10% in the fingernails [168]. The blue discoloration does not disappear with distal pressure on the nail plate. It may be homogeneous within the lunula or more intense in the distal lunula fading proximally. The differential diagnosis of blue lunulae includes other blue-gray discolorations involving the lunula and/or nail bed such as those seen in argyria or as rare side effects of drugs such as phenolphthalein, busulfan, tetracyclines, and antimalarial drugs.

Hemochromatosis

A brownish-bronze skin hyperpigmentation is seen in about 90% of patients and may rarely involve the nails. Koilonychia is reported in 49% of patients and mainly involves the thumb, index, and middle fingers [169]. Koilonychia can appear at any time during the evolution of the disease and does not seem to be affected by treatment. Longitudinal striations, brittleness, and true or apparent leukonychia have also been described, as have splinter hemorrhages.

Renal disorders

Nail clippings from patients with chronic renal failure reveal elevated levels of creatinine; measurement of creatinine in the nail can differentiate acute from chronic renal failure in patients presenting with advanced uremia for the first time [170].
Hypoalbuminemia

Muehrcke's lines
First described by Muehrcke in 1956 as a clinical finding in patients with a chronic severely low serum albumin [171], Muehrcke's lines describe an apparent leukonychia characterized by the presence of two transverse white bands that run parallel to the lunula and are separated from the lunula and from each other by normal pink nail (Figs 15.34, 15.35). The transverse bands, which disappear with pressure applied to the distal plate, are usually found in the second, third, and fourth fingernails and rarely seen on the thumbs.

The pathogenesis of Muehrcke's lines is still uncertain. It is thought to be a vascular compression within the nail bed due to local edema.

Muehrcke's lines are typically seen in several conditions characterized by hypoalbuminemia, including nephrotic syndrome, liver cirrhosis, and severe malnutrition, but they are also a common finding in patients on systemic anticancer treatment [172]. Leukonychia has been reported to disappear when albumin levels return to normal limits and when chemotherapeutic drugs are interrupted. Muehrcke's lines have also been reported in single case reports of patients undergoing treatments with other drugs, in a severely cachectic AIDS patient [173], and in adrenocorticotropic hormone (ACTH)-dependent Cushing syndrome [174]. Muehrcke's lines can occur after heart transplantation, either in patients with transient hypoalbuminemia [175], or in normoalbuminemic patients [176]. Unilateral Muehrcke's lines have been observed after trauma [177].

Renal failure – hemodialysis

Nail changes are very common in patients with chronic renal failure, their severity and prevalence increasing in parallel with duration and severity of kidney disease, and are more common in hemodialysis and transplant recipients [178–180]. The incidence of nail changes seems to be positively related to levels of parathyroid hormone (PTH) [181]. Nail changes significantly associated with renal failure and considered specific for the disease are absence of the lunulae and half-and-half nails [182–189].

Absence of the lunula describes the absence of the white crescent beneath the proximal nail plate, which corresponds to the visible portion of the nail matrix. It has been reported in patients with renal failure, both in hemodialysis (up to 30% of the cases) and in peritoneal dialysis [190], and it is possibly related to chronic renal failure itself and not specifically hemodialysis. Absence of the lunula may in fact reflect a variety of conditions in hemodialysis patients including metabolic changes and anemia. In the case series reported by Saray et al., absent lunulae reappeared in those patients who underwent renal transplantation [183].

Half-and-half nails (Lindsay's nails)

First described by Bean in two patients with azotemia [191], half-and-half nails were better characterized by Lindsay in 1967, who reported this sign as a marker of chronic renal failure [192].

Half-and-half nails represent an apparent leukonychia in which the proximal area of the nail has a white dull discoloration and the distal area, which occupies 20–60% of the total length, is pink or reddish brown with a sharp demarcation line between the two portions (Fig. 15.36). Visualization of the distal red/brown band is enhanced by venous congestion of the digit and decreased by distal pressure on the nail plate (Fig. 15.37). Nail growth does
not induce distal progression of the nail discolorations. The width of the distal band does not correlate with the severity of azotemia. Half-and-half nails are seen in the fingernails and only rarely in the toenails. Males and females seem to be equally affected, although Jamal et al. observed an increased prevalence in males of 2 : 1 [182].

Histologically, the red color in the distal band is due to an increase in capillary density and thickening of their walls [193]. In some cases, the distal band has an intense brown color (brown variant) (Fig. 15.38) which in two biopsied cases corresponded to an increase in melanin in the corresponding nail bed [194]. Nail bed melanin deposition in patients with renal failure can be related to increased plasma levels of melanotropic hormone.

Half-and-half nails occur in about one-third of patients with uremia and are more common in patients on hemodialysis. The intensity of the discoloration does not correlate with blood urea nitrogen or serum creatinine levels and there is no correlation between the appearance of half-and-half nails and the degree of renal function impairment. Half-and-half nails usually persist unchanged and are not influenced by hemodialysis. They may disappear after kidney transplantation.

Half-and-half nails are typical of but not exclusive to chronic renal failure, as they have been occasionally reported in patients with other diseases, including psoriasis and Behçet disease [195]. Distal red nail bed arcs occupying 15–40% were reported in four patients with Crohn’s disease with zinc deficiency [196].

Another nail change reported in up to 20% of patients with renal failure, present both before and after starting hemodialysis, is splinter hemorrhages [183, 185, 197]. Capillary fragility and thrombocyte dysfunction typical of renal failure can be responsible for the occurrence of this sign, which is not related solely to trauma in these patients. However, a study in 2010 on nail changes in hemodialysis patients compared to controls did not find a statistically significant difference in their prevalence between the two groups [186].

Other nail findings occasionally reported in patients undergoing hemodialysis and possibly related to the micronutrient imbalance that occurs in approximately one-third of these patients include Beau’s lines, koilonychia, pale nail beds, and onycholysis [198].

Acute pseudoclubbing of all fingernails followed by onychomadesis was observed in a patient on peritoneal
dialysis 2 months after *Acinetobacter* peritonitis [199]. Case reports of complications of artificial arteriovenous fistula used for hemodialysis include pincer nails, with or without pseudo-Kaposi sarcoma complications, which reversed after fistula ligation [200, 201], and yellow nails [202]. Pincer nails have also been described in a patient with chronic renal failure due to diabetes who was not undergoing dialysis, suggesting that several factors may be implicated in the development of this nail dystrophy in chronic renal failure [203].

Hemodialysis patients may develop bullous dermatoses in photoexposed areas with bullous lesions developing on the dorsal side of the hands and feet [204]. Severe photoonycholysis followed by loss of the nail plates and ulceration of the nail beds may rarely be associated with pseudoporphyria due to hemodialysis (Fig. 15.39) [205, 206].

Tinea pedis and onychomycosis are common in patients undergoing hemodialysis and peritoneal dialysis [183, 207–209]. A study evaluating the prevalence of onychomycosis in diabetic and non-diabetic patients undergoing hemodialysis found culture-proven fungal nail infections in 26.6% of the patients, one-third of whom were affected by diabetes mellitus [207]. Dermatophytes were responsible in the majority of cases. Presence of diabetes and duration of dialysis were the only two factors positively associated with the risk of onychomycosis.

**Calciphylaxis**

Acral necrosis due to calciphylaxis (calcific uremic arteriolopathy) is a rare possible complication of end-stage renal disease. It occurs in both peritoneal and hemodialysis patients and can sometimes occur prior to dialysis. About 30% of the cases are reported in kidney transplant patients. Gangrene may involve fingers and toes (Figs 15.40, 15.41) and has a more favorable prognosis than necrosis in proximal areas [210].

**Nephrotic syndrome**

Yellow nail syndrome has been reported in one patient with minimal change nephrotic syndrome [211]. Muehrcke’s lines due to protein loss and nail bed edema can also be seen.

**Renal transplantation**

Renal transplant patients have a majority of the nail abnormalities seen in chronic renal failure but appear to have a decreased frequency of half-and-half nails, which seem to disappear completely after transplantation [183]. Absent lunula is the most common finding.

Muehrcke’s lines can be seen after renal transplantation [183, 212] and in patients with chronic renal disease on dialysis [183, 213]. In transplant recipients, Muehrcke’s lines were seen in patients undergoing corticosteroid treatment. These patients had nail bed edema not

Figure 15.39 Hemodialysis pseudoporphyria – erosive nail changes.

Figure 15.40 Calciphylaxis. (a) Gangrene. Courtesy of P. Chang. (b) Histology. Courtesy of L. Requena.
decreased by corticosteroids. True leukonychia (punctate or subtotal) can be seen as well. In a reported case series, two of 32 children who had undergone renal transplant presented pigmented transverse bands of the toenails considered to be due to uremia while 34% showed lamellar onychoschizia [214]. Transverse leukonychia has been associated with acute rejection of renal transplants [215]. Other nail changes may be the result of immunosuppression.

Onychomycoses due to dermatophytes and *Candida* are more frequent in renal transplant patients than in controls [212, 216]. Opportunistic infections may occur and involve the periungual skin as has been reported in a case of subcutaneous phaeohyphomycosis with periungual involvement caused by *Exophiala jeaneselmei* [217].

Skin cancers are a well-known complication of kidney transplantation immunosuppression, and precancers and malignant lesions have been reported in about 14% of these patients [218]. A case report detailed the development of a verrucous amelanotic malignant melanoma in the nail bed 7 years after kidney transplantation [219].

### Reproductive system disorders

#### Pregnancy

Nail clippings from the pregnant mother and subsequent analysis may be a valuable tool to screen newborns for intrauterine drug exposure.

The nails usually grow faster during pregnancy and more slowly than normal during lactation [220, 221]. Increased peripheral blood flow induced by estrogens may explain the rapid growth rate. A study of 312 pregnant women showed an incidence of nail changes of 62.8%. True transverse leukonychia was the most common nail sign, seen in 24.4% of the women, followed by ingrown toenails and onychoschizia [221]. Development of lateral ingrown nails (onychocryptosis) during pregnancy may be explained by the increased mechanical pressure and edema in the foot and by a transient increase in the nail curvature, which may recur in any pregnancy [222] (Fig. 15.42). The pathogenesis of the other reported nail changes, most of which resolve post partum, is not easy to explain and possibly related to hormonal changes.

Skin hyperpigmentation is very common in pregnancy and can be associated with longitudinal melanonychia [223, 224]. Longitudinal melanonychia associated with pregnancy usually involves several nails and results from activation of nail matrix melanocytes (Fig. 15.43). It can persist or resolve with delivery.

The vascular proliferations that may occur during pregnancy, influenced by gestational hormones, may localize in the nail bed dermis, producing a band of longitudinal erythronychia [225].

Impairment of maternal cellular immunity may predispose to infections and is possibly the cause of onychomycosis due to the mold *Paecilomyces lilacinus* that developed during pregnancy in a 41-year-old immunocompetent woman [226].

#### Menstruation

Beau’s lines have been associated with dysmenorrhea [227] but they can also occur physiologically with each menstrual cycle. True transverse leukonychia has been associated with menstruation as well. The report of a case of true leukonychia with onset after the first menses...
and temporary resolution during pregnancy further suggests a possible influence of hormones on nail matrix keratinization [228].

**Endocrine disorders**

**Diabetes mellitus**

Nail proteins are subject to non-enzymatic glycation and measurement of fructose and fructosamine values in the nail plate of fingernails allows evaluation of glycemia in time. There is a significant correlation between nail glycosylation and glycosylated hemoglobin as well as fasting blood glucose levels in patients with diabetes. Therefore, nail clippings can be utilized to assess diabetic control over the past 3–5 months. This can be particularly useful in developing countries [229].

Current recommendations in diabetic children are to start proper hygienic measures and foot care early in order to prevent skin complications in adulthood. However, a study evaluating foot care in more than 500 diabetic children and adolescents showed a tendency to poor toenail care with long or bitten/picked toenails [230]. Obese diabetic children frequently suffered from ingrown toenails.

Pseudoacromegaly with large hands and feet and clubbing have been described in congenital generalized lipodystrophy associated with diabetes (Berardinelli–Seip syndrome) [231].

Nail changes in diabetic patients may be secondary to peripheral neuropathy, vasculopathy, trauma, and infections. Mononeuritis multiplex involving both ulnar nerves can result in motor changes and short, fragile, and discolored nails on both hands [232].

Some nail changes disproportionately affect patients with type 1 and type 2 diabetes mellitus and their recognition may prompt study of glucose metabolism.

Periungual telangiectasias are typical of type 1 diabetes and represent an underlying diabetic microangiopathy. They appear as linear telangiectasias due to loss of capillary loops and capillary dilation and are often visible with the naked eye. However, capillaroscopic examination does not show dilated capillaries until the advanced stages of the disease [233]. Nail fold capillary aneurysms, detected by infrared fluorescence videomicroscopy in a high percentage of patients with type 1 diabetes, are an important morphological feature of diabetic microangiopathy [234]. Hemorrhages and ischemic areas may also be observed. Capillary changes can be helpful when differentiating diabetic stiff-hand syndrome and sclerodactyly from other rheumatic diseases [233]. Splinter hemorrhages are common in patients with diabetes.

Capillaroscopy may also be useful to detect the early changes of microangiopathy in children with type 1 diabetes. Capillary abnormalities, seen in about 30% of cases, include an increase in the number of capillaries, irregular distribution, megacapillaries, deformed loops, and intense red background [235]. The presence and degree of capillary changes can be related to the duration
and severity of diabetes. Avascular areas indicate microvascular disease (retinopathy or microalbuminuria) and are usually seen in patients with diabetic complications, while microhemorrhages are common in children with recently elevated HbA1c [236].

A study comparing nail changes in diabetic patients with peripheral neuropathy with those of leprosy patients found nail changes in 55 of 60 diabetics, with increased nail curvature of fingernails or toenails as the most common nail dystrophy (8.3% and 5% of patients, respectively). Longitudinal ridging was the second most common alteration, followed by the flag sign and a nail modification non-specifically called “dystrophy” [237]. The flag sign, seen only in fingernails and characterized by alternating transverse bands of whitish and pinkish discoloration of the nail plate, was seen in 5% of diabetic patients, but was much more common in leprosy patients.

Other nail dystrophies seen in diabetes are caused by inadequate blood supply to the digit and vary depending on the part of the nail apparatus that undergoes transient or prolonged ischemic damage. Temporary or prolonged matrix involvement leads to single or multiple Beau’s lines, pitting, leukonychia punctata or, more rarely, leukonychia totalis [238, 239]. Slow-growing smooth yellow to yellowish green toenails have been described in people with diabetes. They are thickened and excessively curved from side to side. The great toes are most commonly involved and the discoloration is most often evident on the distal aspect of the nails. Yellow discoloration may be due to products of glycosylation, similar to the yellow color of diabetic skin. The toenails of diabetics may show mild surface abnormalities with a seasonal variation and more prominent roughness during the winter. This suggests that environmental conditions together with diabetic microangiopathy and vasomotor dysregulation are involved [240]. Both dorsal and ventral (pterygium inversum unguis) pterygium may be associated with diabetes, resulting from arterial occlusion and scarring of a portion of the nail matrix or of the hyponychium.

Nail bed damage due to decreased vascular supply induces nail bed hyperkeratosis which may possibly predispose to fungal infection. Apparent leukonychia in the shape of Terry’s nails can be observed in patients with adult-onset diabetes especially in younger patients.

Skin complications of diabetes due to ischemia and/or neuropathy can involve the nail with ulceration and gangrene. Neuropathic ulcers, ischemic ulceration of the nail bed, and gangrene are major complications of diabetic feet (Figs 15.44, 15.45). Infections are frequent and are often the most likely cause of foot amputation. Diabetic bullae may localize to hands and feet, with clear, non-scarring spontaneous blisters on the tips of the toes or proximal nail folds of the fingers [241]. Among the skin changes of the hands that are frequently seen in diabetic patients, finger pebbles (Huntley papules or pebbling) may involve the periungual region. They are
seen in about 75% of patients and appear as multiple minute papules grouped on the extensor side of the fingers, on knuckles, and on periungual tissues. They represent a sign of the skin hypertrophy that may occur in diabetic patients [242, 243].

Both bacterial and mycotic skin infections are common in patients with diabetes mellitus, especially type 2 diabetes. Factors that facilitate onychomycosis and tinea pedis in diabetics include peripheral vascular disease, immunosuppression, trauma, peripheral neuropathy, and age.

Gupta et al. [244] showed that the odds ratio risk for patients with diabetes to have toenail onychomycosis was 2.7 times greater compared with normal individuals. The group also reported that toenail onychomycosis was present in 26.2% of their patients with diabetes. Other studies confirmed these data [245] and reported even higher prevalence of onychomycosis in patients with diabetes, up to 53.3% [246], further increasing when peripheral vascular disease was present [247]. In diabetics, the most common pattern is distal subungual onychomycosis of the toenails and dermatophytes are the usual pathogens. However, in diabetics it is not rare to observe onychomycosis of the fingernails due to Candida (Candida albicans, and less frequently Candida parapsilosis) (Fig. 15.46) indicating an underlying vulnerability to this organism. Onychomycosis has the potential to cause severe complications in diabetics and should be treated promptly [248].

**Hypogonadism**

Reversible onychauxis of the fingernails and toenails has been reported in a man who became eunuchoid after trauma and atrophy of the testicles. The nail dystrophy regressed when androgen levels were restored [249].

**Pituitary disease**

In acromegaly, the excess of growth hormone (somatotropin; GH) induces hypertrophy of the soft tissues of the extremities with an increase in size of fingers and toes and a characteristic blunted shape. Numerous nail dystrophies have been reported, the most common being thickening and hardening of the nail plate (Fig. 15.47) [250]. Other nail changes described in acromegaly include absence of the lunulae, nail brittleness, koilonychia, macronychia, and ingrown fingernails [251]. The exact prevalence of nail dystrophies in acromegaly is difficult to assess because some reports do not report any nail abnormality and because few series have been published in the literature to date [252].

Thin and brittle nails have been noted in three adolescent patients affected by cerebral gigantism (Sotos syndrome) [253].

**Adrenal disease**

In Cushing syndrome, hypercortisolism increases the risk of infections, explaining the possible finding of onycholysis and chronic paronychia due to Candida [254]. Muehrcke’s lines have been described in a patient with ACTH-dependent chronic Cushing syndrome [255].

In adrenal insufficiency, overproduction of ACTH and alpha, beta, and gamma melanocyte stimulating hormone (MSH) cause cutaneous and mucosal hyperpigmentation which may be associated with longitudinal melanonychia of the fingernails and toenails. Skin, nail, and mucosal hyperpigmentation usually precedes other symptoms by months to years. Longitudinal melanonychia may be the presenting sign in Addison disease (Fig. 15.48) and is slowly reversible after replacement therapy [256]. Primary adrenocortical insufficiency may be misdiagnosed as Laugier–Hunziker syndrome when hyperpigmentation principally involves nails and lips and ACTH measurement is not performed [257]. Thin and brittle nails have been reported in a patient with Addison disease with massive hyperpigmentation of the skin and mucosae but not of the nails [258].

**Parathyroid disease**

Nail brittleness and ridging were the most common nail changes observed in a series of 21 patients with hypoparathyroidism, affecting 38% of the cases [259]. Other nail signs seen in that series include onycholysis,
onychoschizia, and onychomadesis. Single case reports of patients with hypoparathyroidism reveal other possible nail dystrophies, i.e., nail atrophy [260], splinter hemorrhages, thinning and onychorrhexis [261], nail shortening and thickening [262], and transverse leukonychia [263]. Nail changes seen in hypoparathyroidism can be directly correlated with the serum calcium levels and usually disappear when the serum calcium is restored to normal. It is postulated that hypocalcemia induces nail alterations due to angiospasm and disorganization of the hard keratin and of the integrin subunits [263].

Nail brittleness and Beau’s lines can occur after a severe attack of acute hypocalcemia. Shedding of the nails (onychomadesis) and necrosis of the nail beds have also been described, perhaps as a result of angiospasm.

Brachydactyly is the common feature of pseudohypoparathyroidism, an inherited condition in which hypocalcemia and hyperphosphatemia are associated with increased serum concentration of PTH and insensitivity to its biological activity. Pitted nails and broad thumb were associated with brachydactyly in a 10-year-old child with pseudohypoparathyroidism and chronic papilledema [264].

Pseudo-pseudohypoparathyroidism, which is a variant of pseudohypoparathyroidism without hormonal resistance, may be associated with ingrowing toenails secondary to the soft tissue and skeletal changes.

In hyperparathyroidism, calcium mobilization may induce acroosteolysis. Acquired racket nails (brachyonychia) due to shortening of the distal phalanges can be a presenting sign that leads to diagnosis (Fig. 15.49) [265, 266]. Beau’s lines have been reported in women with hyperparathyroidism with parathyroid adenoma that developed during pregnancy [267]. Nail shedding (onychomadesis) has been reported after treatment with parathyroid extracts [268].

Digital clubbing secondary to hyperparathyroidism is an unusual complication of maintenance hemodialysis therapy in patients with chronic kidney disease [269].

Figure 15.47 Acromegaly: (a) Acromegaly. (b) Radiograph shows anchor-like shape of the lateral aspect of the distal phalanges. Courtesy of D. Wendling.

Figure 15.48 Addison disease: longitudinal melanonychia of several nails was the presenting sign.

Figure 15.49 Hyperparathyroidism: acquired racket nails and koilonychia. Courtesy of B. Schubert.
Thyroid disease

Approximately 5% of hyperthyroid patients have nail changes, with onycholysis and brittle nails as the most common, followed by koilonychia [270]. Onycholysis in hyperthyroidism often takes the shape of Plummer's nails, first described by Henry Stanley Plummer in 1918 in a patient with hyperthyroidism, characterized by a distally concave shape of the nail plate and nail bed detachment. The fourth digits of the hands are initially involved, then the fifth nail, but the alteration may affect any and all of the fingernails and toenails. Plummer’s nails are considered a typical feature of hyperthyroidism, being reversible after treatment [271–274]. They have also been called “dirty nails” as dirt can be trapped under the detached nail plate [275].

Other reported onychodystrophies observed in hyperthyroidism include onychorrhexis, red lunulae, and splinter hemorrhages. In thyroid acropachy, typical of Graves’ disease, hyperthyroidism is associated with the triad of digital clubbing, soft tissue swelling of the hands and feet, and periosteal new bone formation [276]. Transient transverse melanonychia of the fingernails has been reported in a young patient with Graves’ disease and acute liver injury [277]. The real association between hyperthyroidism and melanonychia in this patient is however debatable, as the patient was undergoing radium treatment which is a well-known cause of nail matrix melanocyte activation.

Yellow nail syndrome has been occasionally associated both with hyper- and with hypothyroidism [278].

Hypothyroid patients usually have brittle nails, often with longitudinal and transverse striations and a dull appearance. Onycholysis and slow growth rate are occasionally observed [278–281]. Brittle nails and slow nail growth are also present in congenital hypothyroidism. Thick, hard, and lusterless nails have also been described and may develop while the patient is undergoing therapy for hypothyroidism. Patients with hypothyroidism, in contrast to hyperthyroidism, have significant changes in capillary blood flow velocity. In hypothyroidism, the skin’s microvascular autoregulatory mechanisms are disturbed [282]. Elevated levels of sodium and potassium were detected with laser-induced breakdown spectroscopy (LIBS) in patients with hyperthyroidism [283].

Nervous system disorders

Several diseases of the peripheral or central nervous system are associated with the appearance of a variety of nail dystrophies which are sometimes characteristic, especially when they reflect the area of the nervous system that is damaged. Other nail changes are occasional and reported in single case reports. For example, the literature contains single reports of the yellow nail syndrome associated with mental retardation [284], sleep apnea [285], and Guillain–Barré syndrome [286].

Syringomyelia

Syringomyelia is the development of a fluid-filled cavity or syrinx within the spinal cord, most commonly in the cervical area. It is usually caused by blockage of the cerebrospinal fluid circulation or by spinal cord injuries. Expansion of the cyst impairs neural function producing sensory, motor, and autonomic nerve damage with symptoms corresponding to localization of the damage. Segmental loss of pain and temperature sensation in the hands and arms are the principal clinical features of syringomyelia. Skin signs depend on the defective sensory function but also on impaired vasomotor activity. Repeated minor trauma causes thickening and callousities of the skin on the fingers and knuckles and swelling and edema of the hands. Nails can grow slowly and be dystrophic. Painless ulceration of the fingers and nail folds resembling chronic paronychia is commonly observed (Fig. 15.50). Resorption or spontaneous amputation of the terminal phalanges can also occur [287]. Asymmetrical onychia has been reported in one patient [288].

Hemiplegia

Hemiplegia defines paralysis on one side of the body caused by brain damage, while the term hemiparesis indicates weakness or partial paralysis on one side of the body caused by brain damage. The site of the cerebral vascular accident or other brain injury is usually on the opposite side of the body.

A study on the shape of the thumbnail in 100 subjects with hemiplegia compared to controls showed that the thumbnail of the hemiparetic side in hemiplegia has a greater degree of curvature than that on the contralateral side. This is a sign of the role of mechanical forces in determining the fingernail shape [289].

In hemiplegia, the growth rate of the nails on the affected side is slower and longitudinal (onychorrhexis) and transverse striations or nail plate shedding (onychomadesis) can occur. In a controlled study of 108 consecutive patients with hemiplegia due to stroke, three nail changes were associated with hemiplegia and affected the fingernails of the affected limb: longitudinal reddish striations (in 6%), Neapolitan nails (in 3%), and unilateral clubbing (in 2%) [290]. Nail changes appeared several months after the onset of hemiplegia, with unilateral clubbing following the onset of hemiplegia by an average of 5–10 years. Unilateral clubbing may involve one or more fingers of the affected hand and may be associated with muscular contraction [291, 292]. Its prevalence increases with duration of hemiplegia.
Unilateral pterygium inversum unguis involving fingers and toes of the hemiparetic side has been described in a male patient [293]. A patient with psoriasis developed progressive subungual hyperkeratosis and accelerated nail growth confined to his left hand 2 years after a mild left-sided hemiparesis due to a cerebrovascular event [294].

Spinal cord injuries

Toenail onychogryphosis unrelated to the level of the neurological injury is very common in patients with spinal cord injuries [295]. Ingrown nails are also common, usually after the initial period of bedrest. Patients with tetraplegia appear to be more frequently affected than those with paraplegia. Brittle nails, atrophic skin changes, and toe flexor spasm (Fig. 15.51a) are considered to be the main predisposing factors in the development of ingrown toenails in patients with spinal injuries [296]. Nail dystrophy associated with unilateral hyperhidrosis and callosities appeared in a boy with tethered spinal cord syndrome [297].

Self-inflicted finger injury (autophagia), sometimes resulting in finger amputation, has been described in tetraplegia. Limb autotomy, or autoamputation, may be seen as a response to pain in the targeted limb in subjects under severe psychological and medical stress [298]. A history of mild preinjury obsessive-compulsive behaviors, such as nail biting, is common in these patients.

Unilateral transverse white bands (transverse leukonychia) have been reported to occur on the right ring and little fingernails after C4 complete spinal cord injury [299] (Fig. 15.51b). The bands moved distally as the nails grew out. The proximal newly formed nail in the affected fingers became brittle and dystrophic over a 5-month period.

Congenital absence of pain

There are two varieties of congenital absence of pain: congenital indifference to pain and congenital insensitivity to pain. In congenital indifference to pain, children

![Figure 15.50 Syringomyelia: thickening and callosities of the finger skin, paronychia, and nail dystrophies. Courtesy of C.I. Beylot.](image)

![Figure 15.51 Spinal cord injury: (a) dystrophic periungual skin changes; (b) unilateral nail dystrophy (true leukonychia) 1 month after C4 spinal cord injury. Courtesy of S. Burge.](image)
discriminate painful stimulations but are not able to integrate pain sensation into conscious experience. This is possibly due to a dysfunction in the central structures where pain is integrated. Patients with congenital insensitivity to pain, on the other hand, have abnormalities of the peripheral nerves of central sensory pathways leading to an inability to recognize and avoid noxious stimuli [300]. In congenital insensitivity to pain syndrome with anhidrosis, an extremely rare congenital disorder linked to variants in NTRK1, congenital analgesia is associated with inability to sweat, which leads to defective thermoregulation with recurrent episodes of hyperthermia [301]. Congenital insensitivity to pain also has been reported to be associated with hyperhidrosis [302]. These patients may exhibit normal intelligence and lead productive lives despite failure to experience pain due to broken bones, severe cold, or burns or trauma to the digits. Trauma may lead to gangrene and toes may have to be amputated. Patients with congenital absence of pain usually present with early mucocutaneous signs due to self-biting behavior that first appear at the time of tooth eruption and involve the mouth and hands. Autoextraction of teeth and tongue ulcers are common, as well as periungual ulcerations, nail deformities, and even severe finger mutilations with loss of nails due to chewing of the fingers [303] (Fig. 15.52). X-ray studies of the fingers may show partial resorption of the terminal phalanges.

**Peripheral neuropathies**

Congenital and acquired sensory neuropathies that produce analgesia are frequently associated with recurrent painless acral skin ulcers. Spontaneous amputation of the digits can occasionally occur.

Acropathia ulceromutilans acquisita (AMA or Bureau–Barrière syndrome) is a rare acquired disease of the lower extremities characterized by the triad of painless ulcers, sensitive polyneuropathy, and osteolysis [304]. Upper limb involvement is extremely uncommon [305, 306]. The onset can be precipitated by chronic trauma, alcohol intake, and/or diabetes. Psoriasis may be associated [307, 308]. Trophic ulcers start as blisters on pressure points. Subungal hematoma, progressive distal onycholysis, distal nail splitting, and a shortening of the nail plate (prominent nail atrophy) are associated nail findings. Mutilating ulcers and annular constriction (pseudoainhum) leading to spontaneous loss of the digits frequently occur [309] (Fig. 15.53).

**Unilateral nail changes secondary to anticancer therapy neuropathies**

The integrity of peripheral nerves seems to be necessary for the development of nail alterations secondary to anticancer therapies (see Chapter 17).

**Cervical rib syndrome**

Cervical ribs are usually an incidental finding on the chest radiograph, as they are usually asymptomatic and very short. When they are long and they are linked or fused with the first rib, their presence is associated with vascular symptoms where the brachial plexus, subclavian artery, and/or subclavian vein may be compromised. In arterial thoracic outlet syndrome, the subclavian artery is compromised by a fully formed cervical rib. In true neurogenic thoracic outlet syndrome, the brachial plexus is compromised by a translucent band extending from a rudimentary cervical rib to the first rib. Pain and paresthesia are the first symptoms and may be associated with nail changes, including nail thinning and shortening, grooving, onycholysis, and onychogryphosis. Upper extremity ischemia and finger necrosis can result [310].

![Figure 15.52](image-url) Congenital insensitivity to pain syndrome with anhidrosis: self-inflicted ulcers of the tongue and amputation of the second fingertip.
Chapter 15
510
Carpal tunnel syndrome

Carpal tunnel syndrome is a collection of characteristic symptoms and signs that occurs following compression of the median nerve within the carpal tunnel and damage to its sensory and autonomic fibers. Nail dystrophy usually involves the index and medial fingers and includes Beau’s lines, onychomadesis (Fig. 15.54), koilonychia, striate leukonychia, longitudinal grooves, onychogryphosis, and a diffuse brown discoloration [311, 312]. Atrophy of the thenar eminence is a typical associated finding. Nail signs typically regress after surgical treatment. Severe cases are characterized by nail or fingertip blistering with ulcerations (Figs 15.55, 15.56) and even gangrene with acroosteolysis of the terminal phalanges [313, 314] (Fig. 15.57). The condition can be bilateral.

Poskitt and Duffil [315] reported the case of a 70-year-old man affected by squamous cell carcinoma who developed carpal tunnel syndrome and acrokeratosis paraneoplastica of Bazex. Both conditions improved after treatment of the tumor. In this case, carpal tunnel syndrome was a paraneoplastic phenomenon.

Peripheral nerve injuries

Following damage to the median or ulnar nerves, fingernails can grow more slowly, fingerpads can become atrophic, and nails may appear narrowed and claw-like. Bone density in affected fingers decreases and, in long-standing cases, bones are reduced in size. Nail involvement is uni- or bilateral and reflects the damaged nerves. Its pathogenesis is probably vascular impairment

Figure 15.53 (a) Acropathia ulceromutilans acquisita: pseudoainhum constriction. Courtesy of O. Vanhootegehen. (b) Acropathia ulceromutilans: deep ulcer of the toe. Courtesy of H. Barrière.

Figure 15.54 Carpal tunnel syndrome: onychomadesis of the first, second, and third fingernails.

Figure 15.55 Carpal tunnel syndrome: necrotic eschar of the second fingernail leading to nail destruction.
due to sympathetic innervation damage. Other possible nail changes include onychomadesis, onycholysis [316] (Fig. 15.58), Beau’s lines, and symptomatic pterygium inversum unguis (Fig. 15.59). Onychomadesis and focal hemorrhage from the proximal nail folds of several fingers have been reported after a major central neurological deficit [317]. A case of sympathetic leukonychia in nails adjacent and contralateral to an injured nail has been described [318].

Local injury, such as trauma and fingertip crush injury, can produce Beau’s lines in one or two nails [319, 320]. Beau’s lines and onychomadesis have also been reported after a fractured and immobilized wrist [321, 322] (Figs 15.60, 15.61), and after elbow fracture [323], and sometimes associated with pyogenic granuloma of the proximal nail fold [324–327] (Fig. 15.62). Most of the patients reveal pain during cast wearing, explaining transient nerve damage that results in the appearance of nail symptoms and is often associated with hyperhidrosis 30–40 days after cast removal.

Unidigital clubbing has been described with trauma to the digit or median nerve [328]. Pyogenic granulomas can accompany Beau’s lines in the acute inflammatory polyradiculoneuropathy Guillain–Barré syndrome.

**Complex regional pain syndrome**

Complex regional pain syndrome is a chronic progressive disease characterized by severe pain, swelling, and skin changes for which there is no cure. Complex regional
pain syndrome is divided into two types based on the nerve lesion following the injury: type I and type II [329]. In type I, formerly known as reflex sympathetic dystrophy (Sudeck atrophy, reflex neurovascular dystrophy, algoneurodystrophy), there is no demonstrable nerve lesion. In type II, formerly known as causalgia, there is evidence of obvious nerve damage. Complex regional pain syndrome is distinguished from other chronic pain conditions by the presence of signs indicating prominent autonomic and inflammatory changes in the region of pain. The cause is unknown but it is possibly a post-traumatic neuralgia associated with distal degeneration of small-diameter peripheral axons. The pain of complex regional pain syndrome is constant and may be heightened by emotional or physical stress. Moving or touching the limb is often intolerable. Precipitating
factors include myocardial infarction or traumatic events, such as injury and surgery, although there are documented cases where there is no demonstrable injury at the original site. Wrist fractures are the most frequent causes of sympathetic dystrophy of the hand [330]. Three cases of reflex sympathetic dystrophy after a nail biopsy or surgery have also been reported [331–333]. Changes in the nail growth rate occur in two-thirds of patients with reflex sympathetic dystrophy [334]. Nail signs that have been reported in the different series and case reports include excessive transverse curvature, brittleness, total or partial leukonychia, trachyonychia, Beau’s lines, clubbing, and acute paronychia [333, 335–343] (Fig. 15.63). Acute whitlow-like inflammatory nail changes may result from recurrent atopic dermatitis of the hands [344]. A possible case of reflex sympathetic dystrophy was reported in a patient on peritoneal dialysis who developed changes consisting of acute pseudoclubbing, elkonyxis, Beau’s lines, and onycho­madesis with spontaneous recovery [345].

**Other central nervous system disorders**

Multiple sclerosis is a demyelinating disease in which the fatty myelin sheaths around the axons of the brain and spinal cord are damaged. Multiple sclerosis has been associated with nail plate longitudinal striations and splinter hemorrhages [346]. Multiple system atrophy is a degenerative neurological disorder of unknown cause associated with the degeneration of nerve cells in specific areas of the brain causing problems with movement, balance, and other autonomic functions of the body. In one patient, Siragusa et al. [347] observed fingernail changes consisting of a single, well-defined, transverse, reddish band occupying the central area of the nail.

“Coma nails” or “pen push purpura” is the term used to describe bilateral subungual hematoma from nail bed compression with a pencil exerted by doctors during visits to monitor the patient’s response to pain [348, 349]. Parkinson disease has been associated with an increased nail growth rate and hyponychial hemorrhages. Beau’s lines and onychomadesis may follow a severe epileptic convulsion.

**Poliomyelitis**

The paralyzed limbs of patients with anterior poliomyelitis can exhibit toes or fingers that are considerably diminished in size with slow nail growth. Hyponychial hemorrhages, horizontal ridging, onycholysis, and onycho­madesis have also been described.

**Psychological and psychiatric disorders**

**Onychophagia**

Nail biting (onychophagia) is a common oral compulsive habit that occurs in one-fifth of children and may be also seen in adults as persistence of the habit or as a de novo compulsory disorder. Onychophagia usually starts at the age of 4–6 years, increasing in adolescence [350]. It may evolve from prolonged thumb sucking. When nail biting persists in adult life it is usually severe and associated with a poor prognosis (Fig. 15.64).

Whether nail biting in adults should be categorized as a psychological or psychiatric disease-associated sign is controversial. Some believe that this disorder is related to the obsessive-compulsive spectrum of disorders [351].
Habit–tic deformity is closely associated with nail biting. Affected individuals pick the proximal nail fold of the thumb with the index fingernail, grinding or horizontally stroking the edge of the second or third nail plate across both or the proximal thumb nail plate (Fig. 15.65). Thumbnails are primarily affected, but occasionally all nails may be involved. Habit–tic deformity is often noted incidentally but, unlike patients who bite their nails, affected patients are often not aware of their habit. Other patients admit to continual nail picking but may not realize that they have created the defect. In severe cases, habit–tic deformity results in a longitudinal band of multiple transverse grooves that often have a yellow discoloration extending from the proximal nail fold to the tip of the nail (Fig. 15.65).

Onychotillomania is an unusual obsessive-compulsive psychodermatological disorder in which patients neurotically pick or injure their nails until they are permanently altered. Onychotillomania can be related to a delusion of parasitosis or presence of a foreign body but major depressive illness has also been reported [352, 353]. Occasionally instruments such as toothpicks, scissors, knives, pliers, and razor blades have been used. Patients often deny manipulating their nails but some may either admit to it or relate an unreliable explanation. The clinical presentation of onychotillomania can mimic other nail disorders or have bizarre features. Changes may be relatively minor and present as onycholysis, subungual splinter hemorrhages, or frank hematoma. There may be nail plate scratches or irregular depressions made with gouging instruments. The destruction may be so severe as to lead to scarring and pterygium (Fig. 15.66). If the corners of the nail plate are manipulated, ingrown toenails and/or fingernails can result. Longitudinal melanonychia is common. Secondary infections of the nail may progress to osteomyelitis.

Evaluation of the underlying psychological condition should be carried out [354]. Possible interventions include behavioral therapy and fluoxetine and its derivatives. Local treatments include physically covering the nails with bandages or glue to prevent further trauma [355].

Schizophrenia

Visibility of the nail fold vascular plexus appears to be a genetically transmitted marker for susceptibility to schizophrenia. Plexus visualization scores in people with schizophrenia are significantly correlated with negative behavior, cognitive and motivational deficits, family history, and duration and severity of schizophrenia [356]. A recent article, however, did not find such correlations [357].
Anorexia nervosa and other eating disorders

Brittle nails are reported in about 30% of cases of anorexia nervosa [358, 359] (Fig. 15.67). Other reported nail signs include longitudinal striae, onychocryptosis, and periungual erythema. Nail changes may be due to the hypothyroid state that results from starvation. Severe onychophagia is also common as one of the self-agressing behaviors seen very often in young patients with eating disorders.

Musculoskeletal disorders

Osteoarthritis

The prevalence of nail changes in 102 patients with osteoarthritis of the hand was reported as 13.7% [360]. Longitudinal lines (onychorrhexis) were the most frequent nail alteration and accounted for 10/14 of the observed changes (Fig. 15.68). Nail involvement was associated with long-lasting symptoms related to osteoarthritis and high serum iron concentration. Local primary interphalangeal osteoarthritis of the hand has been reported to produce leukonychia (Fig. 15.69), longitudinal grooves, and nail ridging (onychorrhexis), probably secondary to direct pressure on the nail matrix or local blood flow interference [361]. Nail changes improved with local treatment using non-steroidal anti-inflammatory agents and local corticosteroid injection.

Heberden’s nodes are hard or bony swellings that can develop in the distal interphalangeal joints as a sign of osteoarthritis. They are caused by the formation of osteophytes of the articular cartilage. Nail matrix compression occurs when the nodes become inflamed and results in the appearance of a depression of the nail plate [362].

Digital myxoid cysts are frequently observed in osteoarthritis.

Still disease

Adult Still disease is a rare type of inflammatory arthritis that features fevers, rash, and joint pain. Splinter hemorraghes of the nails were seen in two children with a pruritic linear erythematous rash, intermittent arthralgias, and spiking fever that fulfilled the criteria for adult Still disease but not for juvenile idiopathic arthritis [363].

Figure 15.67 Anorexia: thin and brittle nails.

Figure 15.68 Onychorrhexis associated with osteoarthritis.

Figure 15.69 Primary interphalangeal osteoarthritis of the second finger associated with true leukonychia.
Chronic recurrent multifocal osteomyelitis

Psoriasiform skin and nail signs are rarely associated with chronic recurrent multifocal osteomyelitis, an autoinflammatory bone disease of children and adolescents characterized by pain with swelling and tenderness of some bones, usually the clavicle and metaphyses and epiphyses of long bones. Psoriasiform skin lesions and palmoplantar pustulosis may be associated with periungual inflammation, onycholysis, and subungual hyperkeratosis with salmon patches of the nail bed and pitting [364, 365].

Hematological and lymphatic disorders

Anemia

Patients with anemia, especially hypochromic anemia, exhibit nail bed pallor. Other reported nail changes in patients with anemia are decreased linear growth rate, thinning and brittleness of the nail plate, lamellar onychoschizia, onychorrhexis, and a reduction or absence of the lunula. Onychomadesis has been described in one patient [366].

Bluish-black discoloration of the fingernails and toenails rarely appears in black patients with megaloblastic anemia [367].

Nail fold capillary abnormalities with enlarged and “bushy” capillaries typical of patients with vasculitis have been described in patients with sickle cell anemia [368].

Koilonychia, or spoon nail, describes a concave nail plate with everted distal and lateral edges creating the clinical picture of a “spoon.” It most commonly affects the fingernails, especially the index and third fingernails. Koilonychia is classically associated with iron-deficiency hypochromic anemia [369–373] or Plummer–Vinson syndrome, but its association with systemic disease is probably overrated and it may be more often associated with local environmental trauma and skin disease.

Polycythemia vera

The nails of patients with polycythemia vera may show a red discoloration of the nail bed or of the lunula. Other possible nail changes reported in two patients include koilonychia and lamellar dystrophy of the nails which improved with treatment of the disease [374]. The uncontrolled red blood cell production typical of polycythemia vera may lead to microvascular circulatory disturbances including arterial and venous thrombotic events with acral necrosis and/or ulcers [375].

Thrombocytopenia

Painful ulceronecrotic lesions can be observed in the distal limbs, especially the toes, in essential thrombocytopenia [376], which may also lead to gangrene of toes and fingers [377].

Splinter hemorrhages have been noted in patients with thrombocytopenia as well as in patients with thrombotic thrombocytopenic purpura.

Hemoglobinopathy

Symmetrical peripheral gangrene can be observed in patients with sickle cell anemia. Phalangeal osteomyelitis has also been described [377].

Cyanosis of the lunulae is a typical sign of nigremia, a rare hereditary disease that is associated with the presence of an abnormal hemoglobin (hemoglobin M) [378].

Hereditary hemorrhagic telangiectasia (Osler–Weber–Rendu syndrome)

Capillary microscopy of the proximal nail fold can be helpful in the diagnosis of hereditary hemorrhagic telangiectasia as it reveals the presence of giant loops between the normal capillaries in 83% of cases [379]. Subungual telangiectasia and splinter hemorrhages can also be seen in these patients (Fig. 15.70).

γ Heavy chain disease

γ Heavy chain disease is characterized by the presence of a structurally abnormal heavy chain devoid of light chains in the serum and urine. It is mainly associated with lymphoproliferative and autoimmune disorders. Cutaneous lesions are the most frequent extrahematopoietic manifestation of the disease. A patient with γ heavy chain disease developed cutaneous nodules, livedo reticularis, and digital necrosis caused by necrotizing vasculitis [380].

Figure 15.70 Hereditary hemorrhagic telangiectasia. Courtesy of L. Juhlin.
Cryoglobulinemia

Rallis et al. [381] reported a case of essential mixed cryoglobulinemia with lower leg ulcerations in which the patient’s fingers and toes were cold to the touch and demonstrated decreased capillary refill. This was associated with purplish discoloration of the distal third of all fingertips, becoming more intense in the proximal nail beds. Splinter hemorrhages, subungual hemorrhage, and bullous purpura can also be seen (Fig. 15.71), as can livedo reticularis, Raynaud phenomenon, and painful digital necrosis.

In a report of 29 patients with mixed cryoglobulinemia, almost all showed nail fold capillary abnormalities including tortuosity and apical enlargement, altered orientation, shortening, and neoangiogenesis [382]. These four types of capillary abnormalities were simultaneously present in 10 patients (37%), suggesting this combination to be a characteristic pattern in mixed cryoglobulinemia.

Plasmacytoma and multiple myeloma

Plasmacytoma refers to a malignant plasma cell tumor growing within soft tissue or bone. The skeletal forms frequently disseminate to multiple myeloma over the course of 5–10 years. Most cases produce a paraproteinemia. Plasmacytoma can present as a subungual nodule (Fig. 15.72) [383]. A 66-year-old patient affected by plasmacytoma with monoclonal IgG light chain gammopathy developed hyalinosis cutis et mucosae and a severe onychodystrophy characterized by onychoschizia and onycholysis [384].

POEMS syndrome (Crow–Fukase syndrome) consists of polyneuropathy with organomegaly, endocrinopathy, M proteins, and skin changes. The skin changes include hyperpigmentation, hypertrichosis, hemangiomia, and skin thickening that resembles scleroderma. Myeloma is the most common plasma cell proliferative disorder associated with POEMS syndrome and is present in more than half of all cases. Clubbing of the fingers is very common. Dispensieri et al. [385] studied 99 patients with POEMS and found finger clubbing in five cases. Other changes reported in POEMS syndrome include Terry’s nails [386] (Fig. 15.73) and total leukonychia [387–389] (reported in 38% of the patients in a series of 23 [390]), acrocyanosis, and Raynaud phenomenon [386, 391].

Figure 15.71 (a) Cryoglobulinemia. (b) Cryoglobulinemia–bullous purpura.

Figure 15.72 Plasmacytoma presenting as a subungual nodule. Courtesy of Y. Shindo.

Figure 15.73 Terry’s nails in POEMS syndrome. Courtesy of J.J. Guilhou.
Multiple myeloma can present as one or multiple tumors involving the nails and digits of the hands [392] and may represent the initial symptom [393]. Digital ischemia can occur due to cryoglobulins in multiple myeloma. Other nail changes seen in patients with myeloma may be due to the associated amyloidosis.

**Castleman disease**

Castleman disease is a rare disorder characterized by localized or diffuse lymph node swelling frequently associated with paraneoplastic skin and mucosal diseases [394].

Paraneoplastic pemphigus mimicking erosive lichen planus may be observed in patients with Castleman tumor and nail involvement leads to nail bed erosion with scarring [395–397] (Fig. 15.74). Non-cicatricial lesions regress after surgical removal of the tumor. Paraneoplastic pemphigus associated with Castleman tumor has also been reported in childhood with features of acute violaceous paronychia and onychomadesis [398].

POEMS syndrome has also been associated with Castleman disease [399].

**Leukemia**

Pallor of the nail bed due to anemia can be observed in patients with leukemia. Splinter hemorrhages as well as subungual and periungual hematomas can also be observed. Red lunulae have been reported in myeloid leukemia.

Leukemic infiltration may involve the bone of the distal phalanges and/or the skin. Bone deposits of myeloid precursors cause acquired clubbing and distal digital periosteal bone destruction associated with nail plate abnormalities [400]. A syndrome resembling

Figure 15.74  (a,b) Paraneoplastic pemphigus involving the nails in a patient with Castleman disease. Courtesy of G. Plewig.
pachydermoperiostosis has also been described in this condition [401]. Leukemic infiltration of the skin of the distal phalanx may give rise to different clinical features including a chronic whitlow with bone involvement [402], pernio-like lesions on the fingers and/or toes [403–408], hemorrhagic bullae on the dorsal aspect of hand and fingers [409], severe nail ingrowth with pyogenic granuloma-like masses [410], and nail bed nodule (Fig. 15.75). Norwegian scabies was the presenting symptom of adult T-cell leukemia in two members of a Japanese family [411] and its frequent observation in adults with T-cell leukemia/lymphoma positive for the human T-cell lymphotropic virus type I (HTLV-I) [412, 413] has raised the suggestion that Norwegian/crusted scabies should be considered a marker of T-cell leukemia/lymphoma [414].

Swollen nail folds mimicking chronic paronychia due to leukemic cell infiltration in chronic lymphocytic leukemia have been reported [415–417] as has fingertip hypertrophy [418, 419].

**Lymphoma**

The nail abnormalities observed in patients with lymphoma may be non-specific or may be a direct consequence of the localization of the neoplastic cells in the nail constituents (Figs 15.76–15.78). In cutaneous T-cell lymphoma, they accompany both the localized and erythrodermic forms.

Onychodystrophy has been reported to occur in 32% of patients affected by Sézary syndrome [420]. The nail changes seen in Sézary syndrome and mycosis fungoides are similar, tend to involve several nails, and are usually non-specific [421, 422]. They include paronychia, trachyonychia, onycholysis and subungual hyperkeratosis with nail plate thickening [423–428] (Fig. 15.77), onychomadesis and yellow discoloration [429–431], and pterygium formation due to matrix destruction [428, 432]. Colvett et al. diagnosed a relapsing fever of unknown origin associated with Beau’s lines as a sign of Hodgkin lymphoma [433].

Nail plate thinning and partial obliteration of the proximal and lateral nail folds involving a single finger were observed in one patient with tumor-stage mycosis fungoides and resulted in anonychia after successful localized radiation [434] (Fig. 15.78).

Red lunulae have been described in Hodgkin disease, lymphosarcoma, reticulosarcoma, and lymphoid
fOLLICULAR RETICULOSIS. Nail lesions due to mycosis fungoides can also be seen in children [435].

Severe digital ischemia and gangrene due to cutaneous T-cell lymphoma have been described [436]. Digital ischemia can also to be the presenting sign in Hodgkin disease [437].

In a review of 50 patients with Hodgkin disease, four patients (three males and one female) had transverse leukonychia [438]. All four patients had from one to three transverse white lines; one patient had a dark brown discoloration of the distal part of the affected nail. All changes were more marked in the fingernails than in the toenails. In these patients, the nail changes reflected a poor diagnosis with death occurring within 4 months of the development of the leukonychia. No relationship between nail anomalies and chemotherapy or radiotherapy was evident.

Nail changes may be the presenting sign of lymphoma as occurred in a 34-year-old woman who noticed the 2-week development of painless swelling on several fingernails and toenails with a blackish-red discoloration and leathery appearance. Nail biopsy and evaluation confirmed T-cell leukemia virus (HTLV)-1 positive cutaneous T-cell lymphoma [439].

Non-Hodgkin B-cell malignant lymphoma induced toenail lesions that clinically resembled onychomycosis, later associated with slowly growing pink tumors in a 70-year-old patient affected by chronic lymphocytic leukemia [440]. Treatment with chlorambucil and prednisolone produced almost complete resolution of the tumors. An elephantiasis-like tumescence of the third left finger associated with multiple nodular lesions on several other fingers and dystrophic nail changes were the unusual manifestations of mycosis fungoides in a 56-year-old patient [441].

Yellow nail syndrome has been reported in patients with lymphoma, including mycosis fungoides [442], mucosa-associated lymphoid tissue lymphoma of the lung [443], and Hodgkin lymphoma [444].

Papuloerythroderma may be the presenting paraneoplastic sign in lymphoma and may be associated with splinter hemorrhages and thrombosed capillaries of the nail folds (Fig. 15.79). Paraneoplastic pemphigus may be associated with non-Hodgkin lymphoma and present with skin lesions associated with paronychia and onychomadesis due to proximal nail fold involvement [445].

Connective Tissue Diseases

Capillaroscopy

Nail fold capillaroscopy is one of the various non-invasive bioengineering methods used to investigate skin microcirculation that can detect early microvascular...
changes in connective tissue diseases. The orientation of proximal nail fold capillaries parallel to the surface of the skin permits the observation of both the arterial and the venous limbs of the capillary. In normal subjects, nail fold capillaries are arranged in parallel rows and appear as fine regular loops with a small space between the afferent and efferent limbs. Mean capillary density in healthy adults is in the range of 7.3–10.3 per millimeter. The parameters evaluated by capillaroscopy are: (i) alteration of density, with loss of capillaries and/or avascular areas; (ii) alteration of capillary length (normal values 200–500 µm); (iii) alteration of shape, with tortuous or branched capillary loops, giant or bushy capillaries; (iv) alteration of arrangement, where capillaries are not in parallel rows but disarranged; and (v) presence of microhemorrhages.

Two major patterns of capillary changes occur in collagen vascular disease:

- The systemic lupus erythematosus (SLE) pattern: tortuous meandering loops, i.e. widened, tortuous, “meandering” capillary loops resembling a renal glomerulus (Fig. 15.80).
- The scleroderma–dermatomyositis pattern: capillary dilation and avascular areas, i.e. enlargement of capillary loops, loss of capillaries, disorganization of the normal distribution of capillaries, “budding” (“bushy”) capillaries, twisted enlarged capillaries, and capillary hemorrhages (extravasates) (Fig. 15.81).

Although capillary microscopy is a useful complementary investigation for the evaluation of patients with collagen disorders, it should not be used as a diagnostic criterion in individual patients. In fact, some of the capillary microscopy abnormalities that are observed in patients with collagen diseases may occur in normal controls. Additionally, capillary changes can also occur in other conditions, including schizophrenia, cystic fibrosis, graft-versus-host disease, diabetes mellitus, congenital heart disease, primary biliary cirrhosis, Down syndrome, and homocystinuria.

**Systemic lupus erythematosus**

Although a wide spectrum of nail abnormalities has been described in systemic lupus erythematosus (SLE) none is sufficiently distinctive to be useful in the diagnosis of the disease [446]. In SLE, as in other collagen vascular diseases, the proximal nail fold is the most important site of change, with erythema, telangiectasias, and microinfarcts [447, 448]. Proximal nail fold and periungual erythema as well as proximal nail fold telangiectasia are statistically more commonly observed in patients affected by SLE [448, 449] (Figs 15.82–15.84). The observation of periungual erythema is a simple and useful way to detect connective tissue diseases in clinical practice [450]. In these patients, close inspection reveals irregular capillary loops without the aid of magnification (Fig. 15.85).
Figure 15.82 Systemic lupus erythematosus: periungual erythema and telangiectasia.

Figure 15.83 Systemic lupus erythematosus: periungual erythema and telangiectasia.

Figure 15.84 Systemic lupus erythematosus: periungual erythema and telangiectasia.

Figure 15.85 Systemic lupus erythematosus: proximal nail fold telangiectasias.
Nail fold capillary hemorrhage can be frequently observed close to and involving the cuticle (Fig. 15.82). A close relationship has been reported between these hemorrhages and nail fold capillary abnormalities [451]. Nail fold inflammation in the form of a chronic paronychia has been reported [452] (Fig. 15.86).

Nail bed changes include onycholysis, which has been reported as the most frequent nail abnormality in SLE, seen in approximately 25–40% of cases [453–455] (Figs 15.87, 15.88). Nail bed hyperkeratosis may be seen both in discoid lupus and in SLE [454]. In the latter, it has been described in association with periungual and palmar plantar hyperkeratosis [456].

Altered keratinization of the nail matrix can lead to Beau’s lines, onychomadesis, longitudinal ridging [455], nail plate thinning [447, 457], punctate or transverse leukonychia, and pitting. In a patient with SLE and transverse leukonychia, the width of the leukonychia correlated with duration and clinical activity of the SLE [458]. Increased transverse or longitudinal nail curvature may occur [449]. Two cases of acquired pincer nails of fingernails and/or toenails subsequent to the development of SLE have been reported [459–461]. In one case pincer nails, defined as “prominent ridged nail deformities,” involved the index and small fingers and regressed with glucocorticoid treatment for SLE [460].
Diffuse, dark blue-black chromonychia associated with longitudinal pigmented bands was found to be present in 52% of 33 black patients with SLE [462]. Longitudinal melanonychia can be seen in patients with SLE [463], and it may be associated with dark discoloration of the periungual skin [464].

Red lunulae have been associated with SLE and may be the presenting sign [457]. They occur in approximately 20% of lupus patients, usually affect all 10 fingernails, and show a complete red discoloration of the lunula [465]. They seem to be associated with periungual erythema or chilblain lupus.

Splinter hemorrhages are observed in SLE patients and appear to be associated with disease activity [448, 449]. When SLE is associated with antiphospholipid antibodies, the formation of platelet thrombi in the smaller vessels may result in multiple subungual splinter hemorrhages [466].

Finger clubbing has been occasionally reported in patients with SLE [467, 468].

Pterygium inversum unguis is a common feature of systemic sclerosis, but it can be seen in patients with SLE [469].

The term “lupus erythematosus unguium mutilans” describes a rare destructive involvement of the nails associated with decalcification and atrophy of the distal phalanges [470]. Small vessel necrotizing vasculitis indicative of an underlying vasculopathy can lead to periungual ischemic lesions presenting as focal nail fold infarcts, necrosis, and cuticular hemorrhages. Infarcts in the matrix can lead to permanent nail plate dystrophy (Fig. 15.89). Digital ulcerations and/or gangrene are uncommon in SLE and even if they represent clinical manifestations of cutaneous vasculitis, they are not necessarily related to systemic involvement [471, 472]. In one patient, digital ulcers and Raynaud phenomenon were the initial presentation of SLE [473]. When SLE is associated with antiphospholipid antibodies, digital ischemia and digital gangrene are common (Fig. 15.90) [474, 475].
In SLE, capillaroscopy typically shows the tortuous meandering loop, which is non-specific (see Fig. 15.80). It is seen in 42% of patients with SLE but can also be seen in Raynaud phenomenon and schizophrenia [476]. Nail fold capillary microscopy shows a normal density of capillary loops but marked deformation and disorganization of individual capillaries, with tortuous, meandering, bizarre, ramified, and/or bushy capillaries [477]. The severity of capillaroscopy changes correlates with disease activity [477–479].

Patients with SLE and anticardiolipin antibodies (ACA) also present with capillary abnormalities that are seen in a higher percentage of patients than in SLE without ACA [480, 481]. In SLE, direct immunofluorescence of the proximal nail fold shows the typical lupus band test [482].

**Dermatomyositis and mixed connective tissue disease**

In dermatomyositis, hyperkeratosis of the cuticles is common [483], even in the absence of nail fold abnormalities (Fig. 15.91). Severe cuticle changes with marked thickening and hyperkeratosis associated with periungual erythema and telangiectasia can occasionally be seen [484]. Evolution of the cuticle changes does not necessarily follow that of dermatomyositis. Proximal nail fold erythema and telangiectasia are other typical features (Fig. 15.92) [447].

Gottron’s papules, appearing as erythematous to flattened violaceous papules, typically present on the dorsum of the metacarpophalangeal and interphalangeal joints and may occasionally be seen in the proximal area of the dorsal aspect of the terminal phalanges (Fig. 15.93). Another characteristic hand lesion is the presence of rough and hyperkeratotic skin on the lateral and palmar areas of the fingers, resembling “mechanic’s hands.”

Nail bed splinter hemorrhages can be observed in as many as 10% of dermatomyositis patients [447]. At the hyponychium, pterygium inversum unguis has been reported in two of 19 patients [469]. Red lunulae have been reported. Nail plate changes include thickening, pitting, and trachyonychia. Trachyonychia involving all 20 nails and regressing with disease remission has been reported in a boy [485]. Onychomadesis of several toenails has been described in a patient [486]. Complete nail loss is rare (Fig. 15.94). Periungual ischemic lesions resulting from small vessel necrotizing vasculitis may be a cutaneous manifestation.
of dermatomyositis and their presence might be a predictive sign of malignancy in adult dermatomyositis (Fig. 15.95) [487].

Patients with polymyositis, dermatomyositis, mixed connective tissue disease, and scleroderma have capillaroscopy changes characteristic of the scleroderma–dermatomyositis pattern and show “sausage-like” capillary dilation and vascular dropout (Figs 15.81, 15.96). Tortuosity, deformation, and a bushy appearance of the individual capillaries are frequently associated features (Fig. 15.97). This pattern is fairly specific and present in 90% of scleroderma patients and 82% of dermatomyositis patients. A study on sensitivity and specificity of capillaroscopy in connective tissue diseases showed a high sensitivity of the technique for the diagnosis of systemic scleroderma (89%), a discrete sensitivity for dermatomyositis (60%), and suboptimal sensitivity in SLE (33.33%) and mixed connective tissue disease (20%) [488].

The severity of the microvascular abnormalities parallels disease activity. In childhood dermatomyositis, the presence of enlarged capillaries and avascularity correlated with more severe and persistent forms of the disease [489].

In dermatomyositis, hemorrhages of the proximal nail fold gradually become hemosiderin deposits in the cuticle, an indicator of disease activity [490].

**Systemic scleroderma**

In systemic scleroderma (sclerosis, progressive systemic sclerosis), as in other collagen vascular diseases, the proximal nail fold is the most important site of change. Proximal nail fold erythema and telangiectasias typically occur [447, 448] (Fig. 15.98). Capillary hemorrhages that appear to grow out with the cuticle can be seen as well. The frequency of nail fold bleeding is significantly higher in systemic sclerosis patients than in other connective tissue diseases and controls and is strongly correlated with the presence of anticentromere antibody [491]. Other features seen in the proximal nail fold include chronic paronychia and ragged cuticles. Absent lunula can be observed. Impaired peripheral circulation can lead to nail plate thinning and ridging. Increased nail plate transverse curvature has been associated with increased disease activity [447]. Onychogryphosis can also be observed. Complete destruction of the nail apparatus is the final consequence of the dissolution of the terminal phalanges and occurs in the most severely affected patients.
Parrot beak nail and pterygium inversum unguis are the only distinctive nail changes of systemic sclerosis. Parrot beak deformity (parrot beak nail, nail beaking) is a nail change that develops as a consequence of the atrophy of fingertip soft tissues which characterizes severe acrosclerosis. In parrot beak nail, the nail plate bends around the shortened fingertip (Figs 15.99–15.101). When atrophy of the terminal phalanges occurs, the nail plates become small and brittle.

Pterygium inversum unguis was first reported by Caputo and Prandi, in one patient who did not have any systemic disease [492]. It is characterized by obliteration of the normal distal separation between the ventral surface of the nail plate and the skin of the hyponychium (Fig. 15.102). The resulting adhesion of the fingertip to the nail plate leads to pain when the nails are clipped or after trauma [447, 469]. The most common presentation involves all 10 fingernails but it is often seen with eight fingernails involved, excluding thumbnail involvement. Involvement of the toenails is uncommon [469]. In a review of 19 cases by Caputo et al. [469], pterygium inversum unguis was considered congenital idiopathic in one patient (but this patient went on to develop SLE), acquired but idiopathic in five patients, and secondary in 13 patients. Most patients with the congenital idiopathic form have a positive family history. Patients with the acquired secondary form most commonly have a systemic connective tissue disease, in particular systemic...
sclerosis or SLE. Pterygium inversum unguis was first linked to scleroderma by Patterson [493] and is probably a consequence of the fingertip ulcerations and scarring.

The round fingerpad sign, due to the disappearance of the peaked contour on the fingerpads and its replacement by a hemisphere-like fingerpad contour (Figs 15.103, 15.104), has been described as a useful clinical diagnostic indication of scleroderma [494]. It is most commonly found on the ring fingers and can be seen not only in patients with scleroderma but also in patients with Raynaud phenomenon or mixed connective tissue disease.

Sclerodactyly describes localized thickening and tightness of the skin of the fingers or toes, commonly associated with atrophy of the underlying soft tissues. In a study of 1048 patients with systemic sclerosis, sclerodactyly was observed in 92% [495]. In well-developed cases of scleroderma, the fingers have a tapered appearance due to sclerosis of the overlying skin and frequently exhibit flexion contractures (Figs 15.105, 15.106).

Raynaud phenomenon usually precedes the development of the other cutaneous signs of scleroderma, and swelling of the fingers can be an early symptom of systemic scleroderma.

Although localized scleroderma is not usually associated with nail changes, complete loss of both fingernails and toenails has been reported in a patient affected by acral pansclerotic morphea (Fig. 15.107) [496].

Periungual ischemic hemorrhages and ulceration are frequent in systemic scleroderma (Figs 15.108, 15.109). Digital gangrene is occasionally seen even in the absence of severe systemic involvement (Fig. 15.110). A patient has been reported in whom digital gangrene was the sole cutaneous evidence of systemic sclerosis [497]. Unique digital skin lesions presenting as multiple, soft, dome-shaped tumors along the lateral aspect of the terminal digit.
Figure 15.105  Systemic scleroderma: sclerodactyly.

Figure 15.106  Systemic scleroderma: sclerodactyly.

Figure 15.107  Complete loss of the fingernails in acral pansclerotic morphea. Courtesy of N.R. Rowell.

Figure 15.108  Systemic scleroderma: ischemic changes of the third fingertip.
phalanges of the thumb and index finger were associated with systemic sclerosis [498].

The capillaroscopy changes of the scleroderma–dermatomyositis pattern reveal giant capillary dilation and vascular dropout. This pattern is fairly specific and occurs in 90% of scleroderma patients [499]. These capillary changes are present in most of the patients affected by systemic sclerosis and by its CREST variant, but not in morphea.

Capillaroscopic-guided nail fold biopsy permits the study of different capillary patterns in connective tissue diseases and reveals that the most severe alterations of the microvessels are seen in scleroderma [500].

*Sjögren syndrome*

A case report of a 60-year-old woman with Sjögren syndrome revealed mucocutaneous candidiasis associated with lichen planus-like changes of the fingernails and chronic nail bed inflammation of the nails of the great toes [501].

Capillaroscopic abnormalities in Sjögren syndrome range from non-specific findings to the scleroderma–dermatomyositis pattern. A capillaroscopy score >1 is seen in 50% of the patients, and is more frequent in patients positive for anti-endothelial cell antibodies (AECA) than those without [502], suggesting that AECA are important in the pathogenesis of the endothelial damage in this disease. Sjögren syndrome patients with Raynaud phenomenon presented capillary abnormalities in higher frequency than patients without Raynaud phenomenon.

*Rheumatoid arthritis*

A wide spectrum of nail abnormalities has been described in rheumatoid arthritis. Nail signs were found in significantly more patients with rheumatoid arthritis (52%) than controls (35%). Changes that reached statistical significance were dilated nail fold capillaries, longitudinal ridging (nail beading) (Fig. 15.111), and onycholysis [503]. In a study of nail changes in 50 patients with rheumatoid arthritis and 50 controls, longitudinal ridging was the only nail finding in rheumatoid arthritis in which the association reached statistical significance [504]. The thumbnails and great toenails are more frequently affected. A global pattern of beading on the surface of at least six fingernails or four toenails has been reported to be highly specific for rheumatoid arthritis (predictive value of about 95%). Because nail beading is infrequent.
in the early phase of the disease, the diagnostic value of this abnormality is limited.

Red lunula in fingernails is statistically significantly associated with rheumatoid arthritis and is a frequent finding [447]. A pink or dusky red homogeneous discoloration of the proximal part of the lunula is characteristic (Fig. 15.112). Jorizzo et al. [505] suggested that red lunulae are not a specific manifestation of rheumatoid vasculitis and more closely resemble the palmar erythema associated with rheumatoid arthritis.

Splinter hemorrhages are another frequent finding [447]. Other reported nail changes in patients with rheumatoid arthritis include a white, dull-colored nail plate, onychogryphosis, clubbing, koilonychia, increased transverse curvature, and pitting [503, 506].

Bywaters in 1957 [507] first described the association of small nail fold and pulp hemorrhagic lesions due to necrotizing vasculitis in patients with rheumatoid arthritis (Figs 15.113, 15.114). These small painless infarcts of the nail fold are a characteristic feature of rheumatoid patients. Chronologically, these lesions first appear as periungual swelling, then skin infarcts and necrosis develop, followed by eschars, which usually disappear within a few days without scarring and this eventually results in grooving of the nail. Fingernail gangrene is rare, often starts as large hemorrhages and bullae, and indicates the most severe form of rheumatoid vasculitis (Fig. 15.115) [508].

Rheumatoid nodules can be localized to the terminal pads of the fingers and the free edge of the nails (Fig. 15.116). Rheumatoid nodules are reported in about
20% of patients with rheumatoid arthritis. A sudden increase in the number, size, and distribution of the rheumatoid nodules, which might be associated with vasculitic lesions on the nail folds, may occur after methotrexate treatment [509–511] and may also occur in systemic-onset juvenile rheumatoid arthritis [512].

Rheumatoid arthritis is the autoimmune disease most frequently associated with yellow nail syndrome [513]. Two types can be defined: spontaneous or the more common therapy-related type. Therapy-related yellow nail syndrome in rheumatoid arthritis is essentially due to d-penicillamine or bucillamine. Many of the rheumatoid arthritis patients reported to have yellow nail syndrome are on these medications and the yellow nail syndrome manifestations improve in many when the medication is withdrawn, suggesting that their condition is mainly therapy related.

A study comparing capillaroscopy findings in rheumatoid arthritis, psoriatic arthritis, and psoriasis without signs of arthropathy revealed that in rheumatoid arthritis the diameter of the arterial and venous limb and of the loop is significantly higher than in the other two conditions, possibly indicating an early manifestation of microvascular damage [514].

Antiphospholipid antibody syndrome

Splinter hemorrhages may be seen in antiphospholipid antibody syndrome. Transient ischemic attacks can frequently lead to splinter hemorrhages in association with amaurosis fugax, a monocular visual loss which can be due to emboli, in antiphospholipid antibody patients [515]. Splinter hemorrhages associated with the hypereosinophilic syndrome may be a clinical marker of thrombosis, preferentially involving the central nervous system [516].

Antisynthetase syndrome

Antisynthetase syndrome is characterized by lung disease, polymyositis, Raynaud phenomenon, and polyarthritis. Antiaminoacyl-transfer RNA synthetase antibodies are characteristic, the most common being anti-Jo1. Periungual ischemic lesions and finger necrosis due to severe arteritis have been reported [517].

Granulomatosis with polyangiitis (Wegener granulomatosis)

Periungual ischemic lesions resulting from small vessel necrotizing vasculitis may reflect the underlying vasculopathy of collagen vascular disease and may be a cutaneous manifestation of granulomatosis with polyangiitis. Small nail fold and pulp hemorrhagic lesions due to necrotizing vasculitis (Bywaters lesions) can also be seen. Vasculitis may result in splinter hemorrhages [518, 519] and subungual purpuric lesions (Fig. 15.117) [520]. Capillaroscopy of the proximal nail fold may show avascular areas [521].

Periarteritis nodosa

Ischemic lesions of the periungual and distal tissues of fingernails and toenails may be a cutaneous manifestation of periarteritis nodosa, resulting from small vessel necrotizing vasculitis. These lesions may rarely result in digital gangrene [522]. Vasculitis may result in splinter hemorrhages.
Fingernail and toenail plate thinning, splitting, and excessive ridging associated with a blue-red rash on the distal fingers and toes have been reported in a patient affected by benign cutaneous periarteritis nodosa (Fig. 15.118) [523].

**Microscopic polyarteritis**

Microscopic polyarteritis is a systemic small vessel vasculitis that primarily involves the kidneys. The lung, nervous system, and skin can also be affected. Ecchymotic lesions and hemorrhagic crusted macules and papules may affect periungual tissues [524].

**Multicentric reticulohistiocytosis**

Multicentric reticulohistiocytosis is a rare disorder characterized by papulonodular skin lesions, disabling polyarthritis, and a typical dermal infiltration of histiocytes and multinucleated giant cells. Half of affected patients may develop wart-like, dark-red to flesh-colored nodules arranged around the nail folds of fingers in a “coral bead” configuration [525, 526] (Fig. 15.119). Similar lesions were also seen in a child with multicentric reticulohistiocytosis [527].

Nail changes described in these patients include brittleness, longitudinal ridging, hyperpigmentation, and atrophy. Joint destruction leads to shortening of the distal phalanges with development of racket nails [528].
Follicular mucinosis (alopecia mucinosa)
Thickened, brittle, and ridged nail plates of all 20 nails were reported in association with follicular mucinosis [529]. Histology revealed a nail hollowed out by cavities running parallel to the surface and filled with amorphous material stained by mucicarmine and periodic acid–Schiff (PAS). In the nail bed, a dense lymphohistiocytic cell infiltrate that resembled the perifollicular infiltration separated the basal layer from the overlying keratinocytes.

Fibroblastic rheumatism
Fibroblastic rheumatism is a rare syndrome characterized by the association of symmetrical polyarthritis and multiple skin nodules. Firm, flesh-colored or yellowish cutaneous nodules measuring 0.5–1.0 cm in diameter are located mostly over the extensor aspect of the fingers (Fig. 15.120) [530]. Sclerodactyly and Raynaud phenomenon can also occur [531]. The pathognomonic histological picture of the skin nodules reveals fibroblastic proliferation and fibrosis with thickened collagen bundles that are arranged in a “whorl-like” pattern.

Reiter syndrome
Reiter syndrome (reactive arthritis) is an autoimmune arthritis that develops in response to an infection and is characterized by an inflammatory arthritis of large joints, conjunctivitis or uveitis, urethritis, and a complex of psoriasis-like skin lesions, including circinate balanitis and keratoderma blennorrhagica. Nail changes may appear identical to psoriasis although they are much less frequent. Nail pitting is found in Reiter syndrome patients and may reflect a predisposition to the development of psoriasis or psoriasiform lesions conferred by HLA-A2 with B27 [532]. Nail involvement in Reiter syndrome may include painless chronic paronychia, onycholysis, subungual hyperkeratosis, and longitudinal grooving and ridging of the nail plate [533, 534]. A case report associates Terry’s nail with Reiter disease [535].

Kawasaki disease (mucocutaneous lymph node syndrome)
Kawasaki disease is an acute febrile systemic vasculitis of unknown etiology largely seen in children from 6 months to 10 years of age, being rare in adults [536, 537]. Reversible nail changes are very common and vary during the course of the disease. Up to 75% of children in the subacute phase of Kawasaki disease show an orange-brown transverse chromonychia of all 20 nails that starts to appear between the fifth and eighth day of onset of fever [538, 539]. The orange discoloration involves the distal half or third of the nail and migrates distally as the nails grow, disappearing after 2–4 weeks. It is better appreciated in the fingernails. The orange color corresponds at onychoscopy to nail bed erythema and closely spaced splinter hemorrhages [540]. Onycholysis may be associated. Transient leukonychia may be a sequela. Leukonychia striata has been described independently of orange-brown chromonychia and may be partial, with discoloration localized to the proximal part of the nail [541–543].

Desquamation of the periungual skin is common and pathognomonic; it appears the fourteenth day after the chromonychia (Fig. 15.121). It involves fingers and toes.

Figure 15.120 Fibroblastic rheumatism. Courtesy of A. Claudy.

Figure 15.121 Kawasaki syndrome: desquamation of the fingertip, 14 days.
and may be associated with Beau’s lines or onychomadesis. Nail degloving is exceptional [544].

Acquired pincer nails have been described after Kawasaki disease in two children, in one in association with psoriasis [545, 546]. Ischemic necrosis of the extremities is a rare complication [547].

**Immunological disorders**

**Primary immunological deficiency syndromes**

Congenital hypogammaglobulinemias are typically associated with susceptibility to infections. These immunodeficiencies can result in a pyoderma, which can affect periungual tissues and cause acute paronychia.

Selective IgA deficiency is considered the most common primary immunodeficiency and is usually due to a maturation defect in B-cells. Reported nail changes include trachyonychia involving all fingernails and toenails in a 10-month-old boy [548].

Wiskott–Aldrich syndrome is characterized by the triad of thrombocytopenia, atopic eczema, and recurrent infections. Typically, IgM levels are low, IgA levels are elevated, and IgE levels may be elevated. Acute paronychia as well as nail pitting and transverse ridging due to atopic eczema can occur. Intense scratching results in a polished shiny surface of the nails.

Job syndrome (hyper-IgE syndrome) combines the features of elevated IgE levels, eczematous skin lesions, and recurrent cold staphylococcal abscesses. Chronic *Candida* infection of the fingernails with paronychia and nail atrophy occur [549].

Severe combined immunodeficiency (bubble boy syndrome, Glanzmann–Riniker syndrome, thymic alymphoplasia) is a genetic disorder in which there is a severe defect in both the T- and B-lymphocyte systems. It is known as the “bubble boy syndrome” because these children are extremely vulnerable to infectious diseases. Severe combined immunodeficiency is frequently associated with chronic mucocutaneous candidiasis, pyoderma, and diffuse severe chronic warts unresponsive to therapy [550].

In a report of two sisters with congenital severe T-cell immunodeficiency associated with alopecia and ridging and pitting of all nails, nail changes persisted despite bone marrow transplantation [551].

In a study of heterozygotes for the responsible FOXN1 gene mutation in severe combined immunodeficiency, 39 of the 55 heterozygous subjects showed nail dystrophy, most commonly characterized as koilonychia [552]. Transverse leukonychia, canaliform dystrophy, and Beau’s lines were also found.

Dyskeratosis congenita (Zinsser–Engman–Cole syndrome) is a rare X-linked recessive pancytopenic disorder characterized by the triad of leukoplakia, poikiloderma, and nail dystrophy. Nail dystrophy is present in 83% of the cases and can be the first sign of the syndrome [553]. Dystrophic nail changes include longitudinal splitting (Fig. 15.122) with pterygium, atrophy, koilonychia, and onychomadesis [553–556].

Multiple carboxylase deficiency is a group of disorders characterized by impaired activity of certain enzymes that depend on biotin. Biotin supplementation may prevent complications. Variable T- and B-lymphocytic deficits and unresponsiveness to *Candida* antigen characterize these deficiencies [557]. In biotin-responsive multiple carboxylase deficiencies, *Candida* paronychia and onychodystrophy may occur.

Chronic mucocutaneous candidiasis is characterized by persistent *Candida* infection of the skin, nails, and mucous membranes and is associated with a defect in cell-mediated immunity that may either be limited to *Candida* antigens or be part of a more general immune abnormality. Nail involvement can occasionally be the sole manifestation of the condition. *Candida* invasion of the nail plate produces a thickened, distorted opaque and fragmented nail plate (Fig. 15.123) with chronic paronychia. Dermatophyte and *Candida* infection can be seen together in the same nail. Fingertips can show a bulbous appearance.

**Therapeutic immunosuppression**

Patients on immunosuppressive medications can develop nail infections which include bacterial acute paronychia, onychomycosis due to *Candida* and dermatophytes, and Norwegian scabies. Blistering distal dactylitis due to hemolytic *Staphylococcus aureus* has been described in an adult patient taking high doses of systemic corticosteroids for the treatment of Crohn’s disease [558].
Graft-versus-host disease

Nail changes are observed in about 30% of adult patients [559, 560] and in up to 45% of children [561] with graft-versus-host disease (GVHD). The prevalence of nail dystrophy in adults seems to be related to duration of disease [562], while in children it seems to reflect severe GVHD [561].

Graft-versus-host disease may first appear as acral erythema characterized by reddening of the fingertips and periungual skin [563] (Fig. 15.124).

In chronic GVHD, nail changes closely resemble nail lichen planus with longitudinal ridging, nail thinning, splitting, roughness, partial or complete nail atrophy, and pterygium [562, 564, 565] (Figs 15.125–15.128). Immunophenotyping of the inflammatory infiltrate within the nail shows prevalence of T-suppressor lymphocytes and epidermal expression of HLA-Dr (Ia) antigens [566].

Other reported nail changes include superficial ulcerations of the lunula (elkonyxis), koilonychia [567], nail plate opacification, onychogryphosis, onycholysis, and longitudinal erythronychia [568, 569]. Scleroderma-like GVHD can result in cuticular telangiectasia.

Secondary fungal infections are common. White superficial onychomycosis due to Trichophyton rubrum was the initial cutaneous presentation of chronic GVHD in a patient reported by Basuk and Scher [570].

Behçet disease

Proximal nail fold capillary microscopy in patients with Behçet disease frequently reveals non-specific findings, mainly consisting of enlarged capillaries and hemorrhages [571]. Subungual flame-shaped hemorrhagic lesions have also been described and are probably due to nail bed vasculitis [572, 573]. Half-and-half nails have been reported in some patients with Behçet disease and possibly result from the systemic vasculitis that characterizes this disease [574, 575]. Severe small vessel vasculitis may rarely cause necrosis of the distal digits [576, 577].

Histiocytosis X

Nail changes in histiocytosis X (Langerhans cell histiocytosis) are rare and involve fingernails and toenails. They may precede the onset of other symptoms [578–580]. Reported nail lesions include periungual inflammation with paronychia, onycholysis with or without redness, subungual hyperkeratosis with hemorrhages and pustule formation or whitish discharge, elkonyxis, purpuric striae, and onychogryphosis [581–590] (Fig. 15.129).

Figure 15.123  Chronic mucocutaneous candidiasis.
Severe pulmonary involvement may be associated with clubbing [591].

Nail lesions have the same histopathological characteristics as skin lesions [592] and have been considered to represent an unfavorable prognostic sign [588]. However, some of the reported cases have remitted spontaneously [593] or responded to treatment [594]. Nail changes have been reported to recur when the disease progresses [588].

The fact that nail involvement by Langerhans cells is usually multiple suggests that the abnormal cells preferentially distribute to these tissues [595].
Low interleukin-2 level

This is caused by deficient interleukin-2 secretion by phytohemagglutinin-stimulated mononuclear leukocytes. A 21-year-old woman with a lifelong history of widespread friable vascular nodules and plaques resembling chronic mucocutaneous candidiasis had thickening and induration of the proximal and lateral nail folds, suggesting chronic paronychia [596]. Cultures revealed *Candida* infection.

Infections

**Human immunodeficiency virus diseases and the acquired immune deficiency syndrome**

In a study of 155 HIV-positive patients, nail changes were found to be present in 67.7% versus 34.0% of controls ($p < 0.001$) [597]. Besides onychomycosis, where the prevalence was related to the degree of immunosuppression, other nail changes included leukonychia, longitudinal melanonychia, Beau’s lines, onychoschizia, and clubbing. An increase in the growth rate of both hair and nails has also been reported [598]. Onychophagia and onychotillomania are probably common in patients with AIDS [599].

Periungual erythema is a typical feature of HIV infection, occurring in 2–4% of patients. It can involve the fingers and toes and may be painful [600, 601]. Capillary microscopy of these lesions shows only dilated capillaries and pathology reveals an increased number of dilated blood vessels in the superficial dermis [602]. The pathogenesis of periungual erythema in AIDS is controversial. Angiogenic factors have been implicated and are thought to be a direct result of HIV infection or possibly due to secondary immunological changes [602]. A wide spectrum of antibodies is found in HIV-infected patients and periungual angiogenesis may occur in a similar manner as in lupus erythematosus or dermatomyositis [603]. Virally-induced liver impairment associated with HIV has been suggested as an etiology due to the presence of viral hepatitis in most of the affected patients [604]. Red finger syndrome associated with necrotizing vasculitis in an HIV-infected patient with hepatitis B is an example of such virally-induced angiogenesis [605]. Beau’s lines in AIDS patients may develop following episodes of severe illness [606, 607].

Loss of the lunula, nail plate thinning and ridging, and onycholysis may be seen [606]. A case report describes a 39-year-old AIDS patient with a lichenoid dermatitis and thin nail plates [608]. The distal border of the lunula was irregular and there were associated longitudinal bands, splinter hemorrhages, and periungual lichenoid papules. Splinter hemorrhages have also been reported in other AIDS series [609].

Acquired digital clubbing in AIDS has been reported in up to 30% of adults [610–612] and in about 20% of children, especially those with pulmonary disease [613–617].

Chromonychia is common in AIDS and includes white, yellow, and brown-black discolorations. Proximal or subtotal leukonychia can be seen in HIV-infected patients [597]. Two children with AIDS were reported with transverse leukonychia after pneumonia and perhaps emotional trauma [618]. Yellow discoloration of the distal portion of some nails is a frequent finding in HIV-infected patients and can be preceded by opacification and loss of the lunulae. Although originally described under the diagnosis of yellow nail syndrome, the yellow discoloration of the nails observed in patients with HIV infection is a different condition and is not associated with the other clinical features of the yellow nail syndrome [619–623]. Yellow toenail changes have been considered together with seborrheic dermatitis, hairy leukoplakia, and oral candidiasis as possible indicators of
progression to established AIDS in HIV-positive patients [624]. Although dermatophytes have been suggested as a contributing factor in the development of yellow nails, bacterial and mycological cultures usually fail to reveal any infectious microorganisms.

Longitudinal, transverse, and total melanonychia in HIV-positive patients is usually caused by AZT (zidovudine). However, gray or brown longitudinal melanonychia of several nails associated with hyperpigmented macules on the palms, soles, and mucous membranes unrelated to AZT treatment has been described in AIDS [625]. The pathogenesis may be related to alphamSH [606, 626].

Bluish to gray banded and distally pigmented fingernails and toenails have also been described in black patients with HIV infection [627–630] and were found to be significantly associated with a CD4 cell count of <200 cells/μL [631, 632].

The rate of nail fold infection is increased in AIDS; fungal, viral, and bacterial infections may occur as well as primary and secondary infection [633]. Acute and chronic paronychia due to Candida albicans are frequently observed [634, 635]. Candida infection can lead to total dystrophic onychomycosis, especially in children with AIDS, where Candida albicans is the major fungal pathogen and causes paronychia often associated with severe nail dystrophy [635]. Mucocutaneous candidiasis is a common manifestation of HIV disease. Both Candida and dermatophyte onychomycosis are frequent in HIV-infected patients, with a cited prevalence of up to 41%, and the incidence parallels the level of immunosuppression [636–639]. Several studies have in fact underlined the possible spontaneous improvement of onychomycosis in HIV-infected patients after initiation of combined antiretroviral therapy [637]. Trichophyton rubrum is the most common pathogen isolated. Fungal invasion may even involve periungual tissues [606, 609, 635, 639, 640].

Proximal white subungual onychomycosis due to Trichophyton rubrum is nearly pathognomonic of HIV infection. This variety of onychomycosis, which is rarely encountered in HIV-negative patients, starts as an irregular white patch that appears from beneath the proximal nail fold and progressively extends distally [641–643]. The infection, more frequent when the CD4+ cell count is less than 450 cells/mm3, may spread to all the fingers and toenails and is caused by Trichophyton rubrum tinea pedis that predate immunosuppression [609]. White superficial onychomycosis due to Trichophyton rubrum may also occur in AIDS, both in adults and in children [643, 644]. Onychomycosis due to non-dermatophytic molds is also common in AIDS and includes pathogens such as Scopulariopsis brevicaulis, Fusarium species, and Aspergillus flavus, the last two of which can be found as the source of disseminated mycosis [643, 645, 646]. A case of congenital distal subungual onychomycosis due to Fusarium oxysporum acquired in utero by a HIV-positive mother has been reported [647]. Pityrosporum ovale was the only microorganism isolated in two patients with AIDS who presented with total dystrophic onychomycosis of all fingernails [643].

An unusual presentation of cryptococcal whitlow (Fig. 15.130a,b) in an HIV-positive patient has been reported by Verneuil et al. [648]. The culture was positive for Cryptococcus neoformans serotype D and the lesion resolved with fluconazole 400mg/day over a 2-month period.

Viral disease is common in AIDS. Periungual warts are common, widespread [649], and recurrent. Biopsy should be performed to rule out the possibility of human papillomavirus (HPV)-induced squamous cell carcinoma. Warts may undergo partial/total spontaneous regression after initiation of antiretroviral therapy.

Herpetic infection in immunocompromised patients presents an atypical clinical picture including painful ulcerative, hyperkeratotic, crusted, and/or necrotic lesions and bacterial superinfections (Fig. 15.130) and diagnosis may be delayed [650–652]. Herpes simplex infection is often complicated by necrotic herpetic finger gangrene [652, 654], and even amputation of the distal phalanx. Severe herpetic whitlow may be the first sign of the disease and may present in children with AIDS [651].

Finger necrosis in AIDS usually follows unrecognized severe herpes simplex infection but may also complicate Candida albicans skin and nail parasitization [655].

Atypical herpes zoster with hyperkeratotic lesions has been reported (Fig. 15.130d), [656].

Norwegian (crusted) scabies can occur in patients with HIV infection and causes nail bed and plate hypertrophy with subungual crusting [657–659].

Kaposi sarcoma can involve the nail area and have unusual aspects resembling a chronic paronychia (Fig. 15.131a,b) [660].

Cases of subungual squamous cell carcinoma have frequently been reported in AIDS, mostly associated with HPV type 16 [661–663].

In HIV patients, psoriasis is approximately twice as common as in the general population. Nail abnormalities may be associated with widespread skin psoriasis or be the sole manifestation of the disease [664].

Pityriasis rubra pilaris (PRP) can be an unusual cutaneous complication of AIDS [665]. It presents in AIDS with unusual clinical features of nodulocystic and lichen
Figure 15.130  AIDS. (a,b) Cryptococcal whitlow. Courtesy of D. Leroy. (c) Herpetic whitlow in an AIDS patient.Courtesy of M.M.S. Nico and E.A. Rivitti. (d) Herpes zoster in AIDS. Courtesy of M. Casado.

Figure 15.131  AIDS. (a) Kaposi sarcoma, subungual location. (b) Kaposi sarcoma in periungual location. Courtesy of S. Goettmann-Bonvalot.
spinulosus lesions [666, 667] and has a poorer prognosis than the classic adult type.

A case report of an HIV-positive male described generalized lichen spinulosus accompanied by extensive onychodystrophy [668].

Non-vasculitic neutrophilic dermatosis is a rare complication of HIV infection. In one case, violaceous annular and arcuate bullous lesions with crusting involved the distal thumb [669]. Enelow et al. [670] reported a patient with vasculitis associated with eosinophilia and digital gangrene.

### Infection in other chapters

Please see the following chapters for other types of infection that also affect the nail apparatus.

- Chapter 18: acute paronychia, erysipeloid, prosecutor’s wart (tuberculous verrucous cutis), tetanus *Mycobacterium marinum*, tularemia, orf, milker’s nodule.

### Nutritional disorders

Nutritional trace elements can be measured in nail samples and several studies have been carried out to evaluate whether the level of these elements could be correlated with diseases such as autism and childhood asthma [671, 672]. Other studies have evaluated if the nail content of some trace elements parallels levels of inflammation-related markers linked to chronic diseases [673].

#### Malnutrition

Lee et al. studied 5000 persons with malnutrition in a concentration camp and showed a 100% prevalence of nail changes [674]. Reported nail changes were often seen together and were typically reversed by dietary improvement. Increased visualization of the nail onychodermal band was seen in all patients. It appeared as yellowish, straw-colored, parallel fine lines in the free margin of the thickened nails. Seventy-five per cent of the patients showed massive nail fragility with horizontal splitting and koilonychia. The severity of layering correlated with degree of malnutrition. In five cases, an extremely painful condition that may correspond to nail degloving was observed [544, 675]. It started as an acute, painful, subungual hemorrhage of one or more nails followed by longitudinal rupture of the distal nail and peeling off of nail and epidermis which gradually returned to normal after nutritional therapy.

Loss of the cuticle and absent lunulae were other findings, as were pitting, Beau’s lines, punctate leukonychia, and longitudinal melanonychia.

Besides nail degloving, the features reported by Lee et al. are common to other studies on malnutrition and nail fragility is the most common sign [676–679]. Slow nail growth has also been described in malnutrition. Finger clubbing was present in 77% of patients with kwashiorkor and may have been related to diarrhea [680].

**Vitamin A deficiency**

Eggshell nails are very thin, white, and curved over the free edge of the digit. They have been described in vitamin A deficiency [681].

**Pellagra**

Pellagra, caused by a chronic lack of niacin (vitamin B3) in the diet, can be associated with half-and-half nails that regress after recovery [682, 683]. Onycholysis, Beau’s lines, and koilonychia have also been reported.

**Vitamin B12 deficiency**

Hyperpigmentation of the extremities, especially over the dorsum of the hands and feet with accentuation over the interphalangeal joints and terminal phalanges, associated with pigmentation of oral mucosa is characteristic of vitamin B12 deficiency [684–687]. Uniform nail hyperpigmentation as well as longitudinal or transverse pigmented bands have been reported [688]. It has been suggested that vitamin B12 deficiency results in a decreased amount of intracellular-reduced glutathione which normally inhibits tyrosinase activity in melanogenesis [684, 687].

**Vitamin C deficiency**

Subungual splinter hemorrhages may be a sign of scurvy, associated with the typical cutaneous manifestations of vessel fragility [689].

**Zinc deficiency**

Zinc deficiency can be due to acrodermatitis enteropathica or acquired. Acrodermatitis enteropathica is a rare autosomal recessive disease due to mutation of the gene SLC39A4 (solute carrier family 39 [zinc transporter], member 4) that induces the inability to absorb sufficient zinc. Diarrhea, alopecia, and acral and periorificial dermatitis are the characteristic manifestations of the disorder. Distal skin involvement induces marked erythema and swelling of the periungual tissues with Beau’s lines,
onycholysis, and subungual hyperkeratosis and, more rarely, bullae formation.

An acrodermatitis enteropathica-like syndrome may occur in children and adults in different situations characterized by zinc deficiency, i.e. premature breast-fed infants, children with inborn errors of metabolism, and patients on total parenteral nutrition [690, 691].

Transverse paired white bands of apparent leukonychia which resemble Muehrcke's lines of chronic hypoalbuminemia can be observed after recovery from acute zinc deficiency [692]. Because 85% of serum zinc is bound to albumin, the hypothesis that Muehrcke's lines may actually represent a marker for zinc deficiency has been discussed [692]. True leukonychia in longitudinal bands of the fingers has been reported in a woman with zinc deficiency [693]. The discoloration disappeared after zinc supplementation.

**Selenium deficiency**

Children and adolescents receiving enteral and/or parenteral nutrition may show nail changes including fragility and leukonychia [694–696] which resolve after selenium therapy.

**Calcium deficiency**

Punctate or transverse leukonychia has been occasionally associated with hypocalcemia, but the common assumption that punctate leukonychia is a sign of calcium deficiency is a fallacy, as in most cases punctate leukonychia follows nail microtrauma.

**Iron deficiency**

Brittle nails, spoon nails (koilonychia), and longitudinal ridging (onychorrhexis) can be observed in iron-deficiency anemia. The iron content of the fingernails is not an indication of iron levels in iron-deficient patients [697].

**Metabolic disorders**

**Citrullinemia**

Citrullinemia is an autosomal recessive metabolic disorder characterized by an argininosuccinic synthetase deficiency leading to hyperammonemia and an accumulation of citrulline in the blood and spinal fluid. Bonafe et al. [698] reported a case of a 56-year-old woman with hypercitrullinemia with clubbing and half-and-half nails but defined these signs as non-specific and not necessarily related to citrullinemia.

**Hyperoxaluria**

Primary, secondary, or acquired hyperoxaluria is characterized by oxalosis, i.e. the deposition of calcium oxalate crystals in renal and extrarenal tissues. Deposition of oxalate crystals in the cutaneous vasculature is prominent in primary hyperoxaluria and leads to skin changes that include livedo reticularis, acrocyanosis, ulceration, and peripheral gangrene [699]. Extravascular skin deposits in the form of calcified nodules and miliary papules are typical of patients with secondary oxalosis due to renal insufficiency. Subungual oxalate deposits may involve one or more nails and appear as opaque, painless, hard masses resembling subungual hyperkeratosis [700].

**Cystic fibrosis**

Cystic fibrosis is a genetic disorder caused by a mutation in the gene for the protein cystic fibrosis transmembrane conductance regulator, which is required to regulate the components of sweat, digestive juices, and mucus. Patients develop progressive disability, difficulty breathing, lung infections, sinus infections, poor growth, diarrhea, infertility, and early death. Nail clippings from patients with cystic fibrosis show an elevated sodium and chloride content [701].

Digital clubbing has been reported to be present in approximately three-quarters of patients with cystic fibrosis and is often one of the presenting features (Fig. 15.132) [702–706]. Finger clubbing correlates with pulmonary function and infection and is related to the degree of hypoxemia. Progression of clubbing indicates a deteriorating pulmonary state.

The pathogenesis of clubbing in cystic fibrosis is unclear. Possible causes include hypoxia, platelet activation, and release of platelet-activated growth factor.

![Figure 15.132 Cystic fibrosis: finger clubbing.](image-url)
and vascular endothelial growth factor. The evidence that clubbing is reversible after lung transplantation indicates that either the transplanted lungs inactivate a circulating clubbing-inducing molecule or that the diseased lungs produced the presumably causative substance [707].

Color Doppler ultrasound in one patient showed increased thickening of the nail matrix and nail bed and increased blood flow of the nail apparatus [708]. This finding may explain why patients with cystic fibrosis often have nail fold telangiectasia and splinter hemorrhages.

**Histidinemia**

Histidinemia (histidinuria) is a rare autosomal recessive metabolic disorder caused by a deficiency of the enzyme histidase. Thickened nails, indistinct lunulae, onychoschizia, and Beau’s lines have been reported in a patient affected by histidinemia [709].

**Lipoid proteinosis (Urbach–Wiethe disease)**

In patients with lipoid proteinosis, nail growth can be arrested [710].

**Dyslipoproteinemias**

Nail clippings from patients with type IV and V hyperlipoproteinemia contain significant amounts of Sudan IV-positive substances. A relationship between lipids found in the nail plate and the status of circulating triglycerides has been suggested [711].

The most common skin manifestation of dyslipidemia is xanthomas which are firm and non-tender cutaneous deposits of cholesteryl ester-enriched foam cells. Xanthomas are classified as tendinous, tuberous, tuberoueruptive, and plane. All types can occur in the fingers, mainly on the tips, but also in the periungual region. Periungual pseudo-Koénen tumors of the second and third toes have been reported in a patient affected by familial hypercholesterolemia [712]. Verruciform xanthomas create hyperkeratotic plaques and can cause severe nail dystrophy and destruction of the entire nail leading to anonychia [713].

**Fabry disease**

Fabry disease (angiokeratoma corporis diffusum) is a rare X-linked recessive sphingolipidosis which causes an accumulation of glycosphingolipids in endothelial and smooth muscle cells leading to generalized angiokeratomas, paresthesias, renal and cardiac insufficiency, and cerebrovascular complications. Capillaroscopy in Fabry disease shows “bushy” (ramified) capillaries and clusters [714, 715]. Raynaud phenomenon is not unusual in these patients [715]. Painful telangiectatic hyperkeratotic papules can be localized on the distal finger, the pulp of the fingernails and toenails [716]. A “turtle-back” shape of the fingernails and distal purpuric-like border have also been reported in single cases of Fabry disease [717].

**Gout**

Urate crystals may be found in the subungual scales in unstained sections allowing the diagnosis of gout [718].

Gouty tophi can occasionally have a periungual location and cause Beau’s lines or longitudinal furrows due to matrix compression (Fig. 15.133). Tophi can present as periungual white painless masses [719] or as hyperkeratotic lesions causing nail dystrophy, which in one case was misdiagnosed as squamous cell carcinoma [720]. Trauma-induced tophi localized to the tip of a toe presented as an erythematous, crusted, non-healing ulcer [721] (Fig. 15.134).

Onychogryphosis has been reported as a common manifestation of hyperuricemia, occurring in 45–73% of hyperuricemic patients [722]. In hereditary hyperuricemia, the nails can show onychogryphosis, splitting, and

---

**Figure 15.133** Gout: nail plate. Courtesy of L. Simon.

**Figure 15.134** Gout: periungual ulcer due to traumatized tophi.
dystrophic changes [723]. Longitudinal striations, brittleness, and crumbling of the nails have also been described [724].

**Lesch–Nyhan syndrome**

Lesch–Nyhan syndrome is an X-linked recessive disease caused by mutation of the gene encoding hypoxanthine-guanine phosphoribosyltransferase and is characterized by hyperuricemia, mental retardation, spastic cerebral palsy, choreoathetosis, and compulsive self-destructive biting of the lips, fingers, and hands. Finger autophagia and nail biting are common and may lead to self-mutilations, requiring extreme management techniques such as the application of restraints and/or extraction of teeth at an early age.

**Alkaptonuria**

Alkaptonuria is a rare autosomal recessive metabolic disorder caused by the deficiency of homogentisic acid oxidase that leads to deposition of oxidized pigmented homogentisic acid in connective tissues (ochronosis). The clinical manifestations of alkaptonuria include distinctive skin pigmentation (ochronosis), arthritis, and dark urine. Ochronosis may involve the nail bed with a bluish-gray, bluish-black, or brown-green pigmentation that involves the whole nail bed or its proximal part [725–727] (Fig. 15.135).

**Homocystinuria**

Homocystinuria is an autosomal recessive disorder causing abnormal metabolism of the amino acid methio-

**Fucosidosis**

Fucosidosis is an autosomal recessive metabolic disorder caused by a deficiency of the lysosomal enzyme α-L-fucosidase with accumulation of fucose in the tissues. Distal transverse purple nail bands are possible cutaneous features which may result from subungual telangiectasias or angiookeratomas of the distal nail bed [729, 730].

**Porphyria**

The porphyrias consist of several clinical syndromes caused by defects of enzymes needed at various steps of heme synthesis that result in accumulation and increased excretion of porphyrins and their precursors. Increased levels of porphyrins in hair and fingernails have been detected in patients with porphyria cutanea tarda [731]. Nail changes have been reported in different types of porphyria, with photoonycholysis being the most specific [732].

Onycholysis, photoonycholysis, and digital and subungual blistering can be seen in porphyria cutanea tarda (Figs 15.136, 15.137). Splinter hemorrhages can also be seen. Spoon nails (koilonychia) and longitudinal pigmented bands or distal hemitorsiion of the nail plate have been reported [733–735]. Photoonycholysis associated with digital and subungual bullae has also been reported in porphyria cutanea tarda-like syndrome of hemodialysis. Onycholysis was the presenting sign of contraceptive pill-induced porphyria cutanea tarda in a patient [736]. Nail involvement can be a prominent symptom of the disease in black patients [737].

In congenital erythropoietic porphyria (Günther disease), development of photoonycholysis may be very painful. Repeated episodes of blistering may lead to severe mutilating deformities of the fingers [738–740]. In two patients with late-onset congenital erythropoietic porphyria, koilonychia preceded the onset of the skin manifestation [741]. Total leukonychia and opaque blue-gray or brownish fingernails with absent lunulae have also been reported [742].

**Amyloidosis**

Dystrophic nail changes may be the initial and possibly earliest manifestation of both primary and myeloma-associated
systemic amyloidosis [743–752]. They tend to worsen slowly over the course of several years. Occasionally, nail changes may be the only cutaneous sign of systemic amyloidosis [753–756]. Nail abnormalities can closely mimic nail lichen planus. The nails appear uniformly thinned, brittle, longitudinally ridged, and distally split. Due to the longitudinal ridges, nail changes have also been described as trachyonychia [757, 758]. Nail flattening, cracking, crumbling, and even partial or complete anonychia can occur. Splinter hemorrhages are common (Fig. 15.138). Narrow pink longitudinal subungual striations and subungual hematomas have also been reported. Chronic paronychia is unusual [759], as is onycholysis [758] and subungal hyperkeratosis [760, 761], which can be very severe, as has been reported in a patient with subungal verrucous plaques of the thumbs that pathologically corresponded to amyloid deposits. Scleroderma-like diffuse infiltration of the hands, fingertip ulcerations, and nail dystrophy can occur [752]. Smooth, thickened yellow toenails and black nail beds have also been described [762]. Shaw et al. [763] described an inherited autosomal dominant case of macular cutaneous amyloidosis with nail changes consisting of marked thickening (onychogryphosis) and yellow discoloration. These nail changes resolved during the third and fourth decades of life.

At nail biopsy, nail lesions of amyloidosis show typical amyloid deposits detectable in the superficial dermis and around blood vessels in the nail matrix and/or nail bed.
Nail changes associated with solid malignancies

Paraneoplastic nail changes can be observed in several types of carcinomas. Nail lesions typically regress after surgical excision or chemotherapy of the tumor. Some nail changes are well-known paraneoplastic signs, including clubbing, hypertrophic osteoarthropathy, and acrokeratosis paraneoplastica of Bazex and Dupré, whereas others have been only occasionally associated with cancers.

Clubbing and hypertrophic osteoarthropathy

Clubbing and hypertrophic osteoarthropathy are the most common paraneoplastic nail changes [764]. These nail changes have been reported in lung cancer [765, 766] where the development of hypertrophic osteoarthropathy has been related to expression of cyclooxygenase-2, an enzyme responsible for the synthesis of PGE2 by the primary tumor [767]. These changes also occur in patients with nasopharyngeal carcinoma, especially when metastatic [768–771], and rarely in carcinoma of the esophagus [772, 773], breast cancer [774], bladder cancer [775], and other carcinomas of different organs.

Yellow nail syndrome

Patients with carcinomas of the respiratory system can develop paraneoplastic yellow nail syndrome. This occurrence has been described in lung carcinoma [776, 777] and in carcinoma of the larynx [778].

Acrokeratosis paraneoplastica of Bazex and Dupré

Acrokeratosis paraneoplastica is a paraneoplastic syndrome that occurs in association with carcinomas of the upper respiratory or digestive tracts [779, 780]. It may precede the associated malignancy by on average 11 months, disappears when the tumor is removed, and reappears with its recurrence. Nail involvement does not always improve with treatment, in contrast to the other skin manifestations associated with the syndrome [781].

Squamous cell carcinomas of head, neck, and lungs represent 60% of cases of malignant neoplasms [782]. Less commonly associated carcinomas are poorly differentiated carcinomas (16%), adenocarcinoma of the prostate, lung, esophagus, stomach, and colon (8%) and small cell carcinoma of the lung [779]. More rarely, Bazex syndrome is associated with transitional cell carcinoma of the bladder, Hodgkin disease, T-cell lymphoma, carcinoid, thymoma, vulvar carcinoma, liposarcoma, cholangiocarcinoma, uterine adenocarcinoma, and breast cancer [779, 783, 784]. It is typically seen in males older than 40 years of age [785].

The pathogenesis of acrokeratosis paraneoplastica of Bazex and Dupré is not well understood. Several mechanisms have been proposed including cross-reaction between antibodies against the tumor and antigens of...
the skin keratinocytes or basement membrane zone, cellular immune response with cytotoxic effects, tumor production of growth factors for keratinocytes, and zinc and vitamin A deficiencies [784, 785].

Clinically, acrokeratosis paraneoplastica of Bazex and Dupré is characterized by erythematous, violaceous, and keratotic plaques with ill-defined borders that are symmetrically distributed on the acral sites, including hands, feet, ears, and occasionally the nose (Fig. 15.139). Distal edema with vesicle formation is uncommon [786]. Progression of the disease parallels that of the malignancy and leads to involvement of palms, soles, and cheeks and then centripetally to the arms, legs, scalp, and trunk. Palms and soles acquire the aspect of palmo-plantar keratoderma, with hyperkeratosis and fissuring.

The nails are typically the earliest manifestation and are almost always involved [787]. Early on, the nail plates are thin, brittle, and fragile. As the condition becomes more established, nails become thicker, white to yellow, and onycholytic with subungual hyperkeratosis resembling advanced psoriatic nail dystrophy (Fig. 15.140). Onychomadesis may occur [788]. The nail bed is eventually replaced by a smooth epidermis to which the irregular horny vestiges of the nail adhere. The nail folds show an erythematous papulosquamous eruption, predominantly on the dorsum of the terminal phalanges [789]. The toenails are more extensively involved than the fingernails. There may be an associated chronic, sometimes suppurative, paronychia [785]. Skin and nail hyperpigmentation may precede the onset of typical skin lesions [790].

Histopathological changes are non-specific. They may be psoriasiform, showing a mild lymphocytic infiltrate around the upper dermal vessels, mild acanthosis, and hyperkeratosis with scattered parakeratotic foci. In some cases, fibrinoid degeneration in the superficial capillaries is seen. The infiltrate usually contains a few pyknotic neutrophils resembling allergic vasculitis. Other changes

(a) (b)

Figure 15.139 (a,b) Acrokeratosis paraneoplastica.

Figure 15.140 Acrokeratosis paraneoplastica.
reported include eosinophilic hyalinization of individual keratinocytes and scattered vacuolar degeneration [789]. Amino acid analysis of the hyperkeratotic and friable nails showed that they were different from normal nails and other investigated diseased nails showed an increase in the percentage residues of lysine, methionine, and glycine, accompanied by a decrease in arginine, threonine, proline, and cysteine [791].

Treatment with topical drugs used for psoriasis is minimally effective; there are reports of response to oral retinoids [792].

Other nail changes that have occasionally been reported in patients with cancers include onycholysis of the fingernails, reported in two cases of poorly differentiated squamous cell carcinoma of the lung [793, 794], splinter hemorrhages involving the whole nail, described in rectal cancer with hepatic metastasis, and Terry’s nail, reported in pancreatic carcinoma with hepatic metastases. A study of 569 hospitalized patients found a correlation between pincer nails and gastrointestinal diseases (Fig. 15.141) [795], confirming this possible association reported in a case of metastatic adenocarcinoma of the sigmoid colon [796].

In 50% of cases, papuloerythroderma of Ofuji may be the presenting paraneoplastic sign of several cancers [797, 798]. Papuloerythroderma may be associated with splinter hemorrhages and thrombosed capillaries of the nail folds.

When associated with malignancy, acanthosis nigricans can be extensive and extend onto the palm with palmar hyperkeratosis and onto the nail with nail ridging and brittleness (Fig. 15.142). Patchy or complete leukonychia and nail thickening and nail fold verrucosities have also been reported [799–801] (Fig. 15.143). Leukonychia striata (transverse leukonychia) of all fingernails has been reported in a 67-year-old woman with breast cancer [801]. Digital necrosis associated with a lupus syndrome may reveal a breast cancer relapse [802]. A case of facial and nail hyperpigmentation that faded dramatically 3 months after surgery in a patient affected by intestinal leiomyosarcoma suggested possible paraneoplastic melanocyte activation [803].

**Metastases to the nail unit**

Cancer metastases to the nail unit are rare. Two reviews have collected 118 [804] and 133 published cases [805] and since then more cases have been found. Carcinoma of the lung is the most frequent association for metastases to the fingers whereas malignancy of the genitourinary tract is the most frequent association for

---

**Figure 15.141** Pincer nails induced by gastrointestinal malignancy. Courtesy of G.B.E. Jemec and K. Thomsen.

**Figure 15.142** Malignant acanthosis nigricans. Courtesy of H. Baker.

**Figure 15.143** Leukonychia in malignant acanthosis nigricans.Courtesy of A. Puissant.
metastases to the toes [806, 807]. A patient with adenocarcinoma of the rectum who presented with subungual metastatic disease has also been reported [808].

Most important, however, is that in 44% of patients with subungual metastases, the appearance of the subungual tumor was the first sign of a previously unsuspected primary malignancy.

The clinical appearance of the lesion is variable, but the most common morphologies are an erythematous swelling of the distal digit or a red to violaceous nodule that distorts either the nail plate or the soft tissue of the distal digit, or both, and can appear as a subungual bleeding mass. The diagnosis of a subungual metastasis is often not initially considered because the symptoms and appearance of the subungual tumor frequently mimic other conditions. The lesion is often initially mistaken as a painful acute infection.

Patients with subungual metastases have a poor prognosis; their survival following the diagnosis of the subungual tumor is usually only a few months.

References


69 Dos Santos VM. (2016). Titanium Pigment and Yellow Nail Syndrome. Skin Appendage Disord. 1: 197.


The Nail in Systemic Disease


236 Hosking SP, Bhatia R, Crock PA et al. (2013). Non-invasive detection of microvascular changes in a paediatric and adolescent population with type 1 diabetes: a pilot cross-sectional study”. BMC Endocr Disord. 5: 41.


The Nail in Systemic Disease


The Nail in Systemic Disease


Hashimoto H, Tsuda H, Takasaki Y et al. (1983). Digital ulcers/gangrene and immunoglobulin classes complement fixation of Anti-dsDNA in systemic
The Nail in Systemic Disease


490 McBride JD, Sontheimer RD. (2016). Proximal nailfold microhemorrhage events are manifested as distal cuticular (eponychial) hemosiderin-containing deposits (CEHD) (syn. Maricq sign) and can aid in the diagnosis of dermatomyositis and systemic sclerosis. Dermatol Online J. 22(2).


Chapter 15


The Nail in Systemic Disease


The Nail in Systemic Disease


Chapter 15


Chapter 16

Drug-induced Nail Disorders

Bianca Maria Piraccini

Dermatology, Department of Experimental, Diagnostic and Specialty Medicine, University of Bologna, Bologna, Italy

<table>
<thead>
<tr>
<th>CHAPTER MENU</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Introduction, 575</strong></td>
</tr>
<tr>
<td><strong>Antimicrobial agents, 578</strong></td>
</tr>
<tr>
<td>Tetracyclines, 578</td>
</tr>
<tr>
<td>Cephalosporin, 578</td>
</tr>
<tr>
<td>Chloramphenicol, 578</td>
</tr>
<tr>
<td>Clofazimine, 579</td>
</tr>
<tr>
<td>Quinolones, 579</td>
</tr>
<tr>
<td>Roxithromycin, 579</td>
</tr>
<tr>
<td>Erythromycin, 579</td>
</tr>
<tr>
<td>Azithromycin, 579</td>
</tr>
<tr>
<td>Sulfonamides, 579</td>
</tr>
<tr>
<td>Dapsone, 579</td>
</tr>
<tr>
<td>Amoxicillin, 579</td>
</tr>
<tr>
<td>Fluvoxacillin (flvoxacilline), 580</td>
</tr>
<tr>
<td>Ganciclovir, 580</td>
</tr>
<tr>
<td>Emetine, 580</td>
</tr>
<tr>
<td>Sparfloxacin, 580</td>
</tr>
<tr>
<td><strong>Antiretroviral drugs, 580</strong></td>
</tr>
<tr>
<td>Nucleoside/nucleotide reverse transcriptase inhibitors (NRTIs), 580</td>
</tr>
<tr>
<td>Protease inhibitors, 581</td>
</tr>
<tr>
<td><strong>Antifungal drugs, 581</strong></td>
</tr>
<tr>
<td>Itraconazole, 581</td>
</tr>
<tr>
<td>Fluconazole, 581</td>
</tr>
<tr>
<td>Ketoconazole, 581</td>
</tr>
<tr>
<td>Amorolfine, 581</td>
</tr>
<tr>
<td>Ciclopirox (ciclopirox olamine), 582</td>
</tr>
<tr>
<td>Voriconazole, 582</td>
</tr>
<tr>
<td><strong>Antimalarial agents, 582</strong></td>
</tr>
<tr>
<td><strong>Drugs acting on the central nervous system, 583</strong></td>
</tr>
<tr>
<td>Anticonvulstant drugs, 583</td>
</tr>
<tr>
<td>Benzodiazepines, 583</td>
</tr>
<tr>
<td>Tricyclic antidepressants, 583</td>
</tr>
<tr>
<td>Venlafaxine, 583</td>
</tr>
<tr>
<td>Phenothiazines, 583</td>
</tr>
<tr>
<td>Lithium carbonate, 583</td>
</tr>
<tr>
<td>Buspirone, 583</td>
</tr>
<tr>
<td></td>
</tr>
<tr>
<td></td>
</tr>
<tr>
<td></td>
</tr>
<tr>
<td></td>
</tr>
<tr>
<td></td>
</tr>
<tr>
<td></td>
</tr>
<tr>
<td></td>
</tr>
<tr>
<td></td>
</tr>
<tr>
<td></td>
</tr>
<tr>
<td></td>
</tr>
<tr>
<td></td>
</tr>
<tr>
<td></td>
</tr>
<tr>
<td></td>
</tr>
<tr>
<td></td>
</tr>
<tr>
<td></td>
</tr>
<tr>
<td></td>
</tr>
<tr>
<td></td>
</tr>
<tr>
<td></td>
</tr>
<tr>
<td></td>
</tr>
<tr>
<td></td>
</tr>
<tr>
<td></td>
</tr>
<tr>
<td></td>
</tr>
<tr>
<td></td>
</tr>
<tr>
<td></td>
</tr>
<tr>
<td></td>
</tr>
<tr>
<td></td>
</tr>
<tr>
<td></td>
</tr>
<tr>
<td></td>
</tr>
<tr>
<td></td>
</tr>
<tr>
<td></td>
</tr>
<tr>
<td></td>
</tr>
<tr>
<td></td>
</tr>
<tr>
<td></td>
</tr>
<tr>
<td></td>
</tr>
<tr>
<td></td>
</tr>
</tbody>
</table>
Drug-induced nail abnormalities may be occasional, and described only in single case reports, or be consistently associated with intake of a drug. Nail changes caused by drugs are often dose related, appear in temporal relation with drug intake, and usually disappear after its withdrawal. They present with a wide variety of symptoms, depending on the part of the nail apparatus that has been damaged. Some nail changes are asymptomatic and only cause cosmetic problems, whereas others cause pain and discomfort and impair manual activities or patient mobility.

Some drugs may induce or worsen some skin diseases and their associated nail signs. For example, adalimumab, etanercept, and simvastatin can induce dermatomyositis; interferon beta, abatacept, and terbinafine can induce psoriasis; allopurinol can induce drug hypersensitivity syndrome; etanercept, hydroxychloroquine, and salsalate can be responsible for lichenoid eruptions; and tiopronin and penicillamine can induce yellow nail syndrome.

Topical drugs may cause nail side-effects that in most of the cases result from excessive skin absorption or allergic contact dermatitis.

Nail clipping for monitoring previous exposure to drugs or poisons
Nail clippings can be utilized to confirm previous intake of drugs and trace elements or exposure to poisons during the months before examination. In fact, like the hair shaft, nails are biological matrices in which drugs or poisons tend to accumulate. Nails are an interesting resource for the investigation of drug use and forensic studies [1]. Usually, the great toenail is chosen for examination.

We can measure the following drugs in the nail: amphetamines and their metabolite metamfetamine, cocaine and its analytes, opioids, cannabinoids and other drugs of abuse [2, 3], as well as alcohol biomarkers [4]. We can also detect topical and systemic antifungals. Numerous trace elements such as iron, zinc, and selenium [2] can be researched in nail clippings. In the same way, we can confirm poisoning with arsenic, lead, copper, chromium, and thallium by detection of the metal in nail clippings [2].

Nail changes associated with drug-induced erythroderma
In the course of drug-induced erythroderma, we can commonly observe Beau’s lines and onychomadesis. “Shoreline nails” have sometimes been described [5]. They appear as onychomadesis preceded by a transverse band of leukonychia and indicate a defective keratinization of the nail matrix followed by total matrix growth arrest. Pachyonychia has also been observed during erythroderma.

Nail changes and teratogenicity
The occurrence of nail dystrophy in newborns depends on the time of exposure during pregnancy and the dose of the teratogen. Hypoplasia of the fingernails and terminal phalanges of the fingers and sometimes the toes can occur in children whose mothers have been treated with trimethadione [6], hydantoin [7], carbamazepine [8, 9], phenytoin [10], alcohol, and warfarin [11] (Fig. 16.1).Regression of nail hypoplasia was observed during the first months of life in a newborn of an epileptic woman treated with carbamazepine during gestation. Valproic acid has been associated with hyperconvex nails. In infants of women with epilepsy who received valproic acid monotherapy, digital abnormalities with long, thin, partly overlapping fingers and toes and hyperconvex nails have been reported [12].

Webbed fingers (syndactyly) have been reported in fetal hydantoin syndrome and in a newborn whose mother was undergoing chemotherapy for breast cancer with cyclophosphamide, 5-fluorouracil, and doxorubicin (Adriamycin) when she became pregnant [13]. Short fingers and hypoplastic nails are part of the phenotype of newborns from mothers treated with mycophenolate mofetil during pregnancy [14].

Drug-induced photoonycholysis
Photoonycholysis describes light-mediated nail detachment, an uncommon condition that may result from drug intake, porphyria, or pseudoporphyria [15–17]. Spontaneous photoonycholysis is uncommon [18]. Drug-induced photoonycholysis is most commonly caused by tetracycline derivatives, psoralens, and fluoroquinolones and is typically associated with cutaneous photosensitization [19]. Nail changes usually appear...
after more than 2 weeks of exposure to the drug and often follow a photosensitivity reaction in the skin, in Segal’s triad: photosensitivity, nail discoloration, and onycholysis [20]. Onycholysis can also appear independently in the absence of the skin rash and be the sole expression of a photosensitivity reaction [21–23]. Box 16.1 lists the drugs that have been associated with photoonycholysis. The pathogenesis of photoonycholysis is damage to the nail bed epithelium with epidermoly- sis and/or with formation of hemorrhagic bullae.

Four distinct clinical types of photoonycholysis after both antibiotics and psoralens are distinguished, based on the features of nail detachment and the number of digits involved [16] (Fig. 16.2). There is no relationship between different types of photoonycholysis and the responsible drugs [24–30].

- **Type I**: several fingers are involved. The separating part of the nail plate is half moon shaped and concave distally with pigmentation of variable intensity and shows a well‐demarcated proximal border (Fig. 16.3).
- **Type II**: one finger only is affected and a well‐defined circular notch is present, which opens distally and has a brownish hue proximally.
- **Type III**: in the central part of the pink nail bed on several fingers there is initially a round yellow stain that turns reddish after 5–10 days (Fig. 16.4).
- **Type IV**: bullae under the nails have been reported in photoonycholysis due to tetracycline hydrochloride [22] as well as in four types of cutaneous porphyria – porphyria cutanea tarda [31], erythropoietic porphyria [32], erythropoietic protoporphyria [33], variegate porphyria – and in pseudoporphyria [34].

The higher UVA exposure explains localization of photoonycholysis to the second to fifth fingernails and sparing of the thumb and the toenails. Toenail photoonycholysis may be seen in patients staying barefoot in sunny tropical areas [15, 35]. More or less evident subungual hemorrhages are commonly associated, and are the possible cause of the nail discoloration. Most of the patients become aware of their photoonycholysis because they feel pain. Onychodynia is commonly reported with tetracycline derivatives and PUVA [22] and may precede onycholysis by 1–4 weeks [16]. The cause of the pain is unknown but terminal vessels, capillaries, or glomus bodies may play an important role. Delay in the onset of photoonycholysis has been reported in a patient who used inadvertent photoprotection in the form of artificial nails [36].

Re‐ingestion of the drug responsible for photoonycholysis does not necessarily cause a recurrence, as drug intake is usually combined with intense sun exposure to induce photoonycholysis. Protective measures against sun exposure for skin and nails may help in recurrence prevention.

### Pseudoporphyria

Pseudoporphyria (also referred to as drug‐induced pseudoporphyria, drug‐induced pseudoporphyria cutanea tarda, pseudoporphyria cutanea tarda, bullous dermatosis of hemodialysis, and bullous dermatosis in end‐stage renal failure) is a rare skin eruption that bears clinical and histological similarities to porphyria cutanea tarda, but is not associated with elevated porphyrin levels or abnormalities in porphyrin metabolism.

---

### Box 16.1 Drugs reported to induce photoonycholysis. * indicates the drugs that regularly induce this side effect

<table>
<thead>
<tr>
<th>Antibiotics*</th>
<th>Chlorpromazine</th>
</tr>
</thead>
<tbody>
<tr>
<td>Tetracyclines (demeclocycline, doxycycline, lymecycline, tetracycline hydrochloride, oxytetracycline, chlortetracycline)</td>
<td>Dipotassium chlorazepate</td>
</tr>
<tr>
<td>Fluoroquinolones (sparfloxacin, moxifloxacin, pefloxacin, ofloxacin), cephaloridine, clocxacillin, chloramphenicol</td>
<td>8% clobetasol</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Psoralens with sunlight or UVA*</th>
<th>Griseofulvin</th>
</tr>
</thead>
<tbody>
<tr>
<td>Trimethylpsoralen</td>
<td>Icodextrin</td>
</tr>
<tr>
<td>5‐Methoxypsoralen</td>
<td>Indapamid</td>
</tr>
<tr>
<td>8‐Methoxypsoralen</td>
<td>Indometacin</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>UVB</th>
<th>Metopimazine</th>
</tr>
</thead>
<tbody>
<tr>
<td>NSAIDs</td>
<td>Olanzepine</td>
</tr>
<tr>
<td>Diclofenac</td>
<td>Oral contraceptives</td>
</tr>
<tr>
<td>Miscellaneous</td>
<td>Paroxetine</td>
</tr>
<tr>
<td>Acriflavinium hydrochloride</td>
<td>Quinine</td>
</tr>
<tr>
<td>Ariprazole</td>
<td>Sirolimus</td>
</tr>
<tr>
<td>Benoxaprofen</td>
<td>Thiazide diuretics</td>
</tr>
<tr>
<td>Captopril</td>
<td>UVA</td>
</tr>
<tr>
<td></td>
<td>UVB</td>
</tr>
<tr>
<td></td>
<td>Voriconazole</td>
</tr>
</tbody>
</table>

NSAIDs, non‐steroidal antiinflammatory drugs; UVA, B, ultraviolet A, B.
Figure 16.2 Photoonycholysis: (a) type I; (b) type II; (c) type III; (d) type III, late stage.

Figure 16.3 Photoonycholysis, type I: the detachment spares the lateral nail plate and has a distal concavity, with small hemorrhages in the attached nail.

Figure 16.4 Photoonycholysis, type III: the central part of the nail bed on several fingers shows a red-brown discoloration.
The possible causes are listed in Box 16.2. Ultraviolet (UV) exposure seems to be involved in most of the cases. Clinically, pseudoporphyria is characterized by the development of bullae on photo-exposed skin areas such as the dorsum of the hands and feet, forearms, face, and neck. Skin scarring and milia formation are common sequelae. The nails may show different types of photoonycholysis, including type IV, with bullae under the nail plate [34, 37–39]. Drug-induced pseudoporphyria subsides after drug interruption.

### Antimicrobial agents

#### Tetracyclines

In patients taking tetracycline hydrochloride in dosages of 1 g or more daily, yellow fluorescence of the lunulae is seen under Wood’s lamp examination [40]. This fluorescence can be useful for monitoring compliance with treatment. A reddish nail fluorescence may be observed with demeclocycline therapy. Tetracycline and oxytetracycline may also induce a yellow discoloration of the entire nail, associated or not with onycholysis.

Photoonycholysis is a classic side-effect of tetracyclines, with demeclocycline as the most common cause, followed by doxycycline [20, 21, 24–29, 35, 38]. Minocycline has occasionally been incriminated whereas oxytetracycline and tetracycline hydrochloride rarely induce this side-effect. Onycholysis without sun exposure can also occur in patients on tetracycline [41]. In association with photoonycholysis, Beau’s lines and subungual hemorrhages can occur.

Skin and eye pigmentation due to minocycline may be rarely associated with nail pigmentation in the form of a blue-gray discoloration of the proximal portion of the nail bed, as well as longitudinal melanonychia, or diffuse dark hyperpigmentation of the nail plate [42–46] (Fig. 16.5). Pigmentation of the proximal nail fold has also been reported [47]. It has been suggested that an iron chelate of minocycline is the cause of the nail pigmentation, which may require months to years to fade after discontinuation of the drug, and even be permanent.

#### Cephalosporin

A periungual inflammatory reaction mimicking acute paronychia associated with mild onycholysis has been described in two fingers of a patient taking cefalexin (Fig. 16.6). This reaction resolved without residual pigmentation but recurred after readministering the drug [48].

Onychomadesis has been reported in patients on maintenance hemodialysis taking large doses of cefaloridine and cloxacillin [49].

#### Chloramphenicol

Onycholysis and photoonycholysis are rare complications of chloramphenicol treatment.

---

**Box 16.2 Causes of pseudoporphyria**

<table>
<thead>
<tr>
<th>Ultraviolet light</th>
</tr>
</thead>
<tbody>
<tr>
<td>Excessive sun exposure</td>
</tr>
<tr>
<td>PUVA (psoralen ultraviolet A)/ UVA (ultraviolet A)/ tanning beds</td>
</tr>
</tbody>
</table>

**Drugs**

*Non-steroidal antiinflammatory drugs (NSAIDs)*

- Diflunisal
- Ibuprofen
- Ketoprofen
- Mefenamic acid
- Nabumetone
- Naproxen
- Oxaprozin
- Tiaprofenic acid

*Antibiotics*

- Fluoroquinolones
- Nalidixic acid
- Tetracycline

*Diuretics*

- Bumetanide
- Chlortalidone
- Furosemide
- Hydrochlorothiazide/triamterene

*Retinoids*

- Isotretinoin
- Ettretinate

*Miscellaneous*

- 5-Fluorouracil
- Amiodarone
- Carisoprodol/aspirin
- Coca-cola
- Ciclosporin
- Dapsone
- Erythropoietin
- Hormone replacement
- Flutamide
- Pyridoxine
- Sulfonyleureas
- Voriconazole

*Diseases*

- Chronic renal failure/dialysis
- Hepatitis C
- Hepatoma
- HIV infection
- Sarcoidosis
- Sjögren syndrome
- Systemic lupus erythematosus
Drug-induced Nail Disorders

Clofazimine

Clofazimine at high doses has been implicated in the development of reversible brown discoloration of the nail plate, subungual hyperkeratosis, and onycholysis, associated with presence of clofazimine crystals seen at histopathology in the nail plate and nail bed [50]. A case of reversible melanonychia due to clofazimine has also been reported [51].

Quinolones

Quinolones (flumequine, pefloxacin, and ofloxacin) have been implicated in photoonycholysis [52, 53]. Subungal hemorrhage was associated in one case [53]. Beau’s lines were described during treatment with moxifloxacin [54].

Roxithromycin

A brownish discoloration of both thumbs followed by pigmentation of all fingernails has been observed after a second course of roxithromycin [55]. Fingernail onycholysis has also been reported following roxithromycin use [56].

Erythromycin

A yellowish discoloration of the fingernails has been reported during long-term therapy with erythromycin [57].

Azithromycin

Onychomadesis on fingers and toes was seen in a 10-year-old girl after therapy with azithromycin [58].

Sulfonamides

Beau’s lines, onychomadesis, paronychia, partial leukonychia, and reduction of nail growth have been described in patients who developed a photosensitivity reaction during sulfonamide treatment [59]. Trimethoprim–sulfamethoxazole was suspected of causing onychomadesis with nail shedding in the absence of other signs of drug reaction in two cases reported in the literature [60, 61].

Dapsone

As in erythroderma of other etiologies, Beau’s lines have been observed in a 35-year-old woman with borderline lepromatous leprosy who developed dapsone hypersensitivity [62].

Amoxicillin

Fixed drug eruption presenting as painful erythematoviolaceous macules of the subungal and periungal region of two fingernails has been reported after amoxicillin intake [63]. Inflammatory signs subsided after drug
withdrawal and were followed by development of Beau’s lines. Relapses in the same location were seen at a further drug assumption.

Amoxicillin intake has also been associated with periungual erythema [64] and erythema multiforme involving the periungual region (Fig. 16.7).

**Flucloxacillin (floxacilline)**

Gangrene of the fingers may occur after accidental intra-arterial injection of flucloxacillin [65].

**Ganciclovir**

Splinter hemorrhages were noted during treatment with ganciclovir for cytomegalovirus (CMV) infection in a woman with HIV infection [66].

**Emetine**

White nails have been described in patients treated with emetine. Nail atrophy and brittleness can also occur.

**Sparfloxacin**

A blue-black nail pigmentation involving the lunula area of the whole nail was reported in three patients after treatment with the quinolone sparfloxacin [67]. Gradual disappearance of the pigmentation followed drug withdrawal.

**Antiretroviral drugs**

**Nucleoside/nucleotide reverse transcriptase inhibitors (NRTIs)**

**Lamivudine**

Paronychia and pyogenic granulomas affecting the toenails and the fingernails have been reported during lamivudine treatment [68–70] (Fig. 16.8). In one case periungual pyogenic granulomas were associated with multitherapy, including efavirenz, lamivudine, and zidovudine [71].

Longitudinal melanonychia appeared on the fingernails 4 weeks after treatment with 300 mg daily. The streaks disappeared after the drug was stopped and reappeared with reintroduction [72].

**Zidovudine (azidothymidine, AZT)**

Various patterns of nail pigmentation have been described in patients receiving zidovudine, especially in black-skinned individuals, with prevalence reaching 67% (Fig. 16.9) [73–84]. Nail pigmentation is dose dependent and may appear at different times after initiation of therapy; it is reversible when zidovudine is discontinued or the dosage is reduced. Fingernails are usually more commonly affected than toenails. Nail pigmentation may be diffuse or in transverse or longitudinal bands, bluish to brown or black in color. A faint blue pigmentation of the
Drug-induced Nail Disorders

lunulae has also been described. Histological studies have shown that zidovudine-induced nail pigmentation is due to melanin deposition [75, 80].

Increased nail growth has also been reported [81]. In a 4-week-old baby treated with zidovudine following perinatal HIV exposure, severe paronychia of the great toenails due to *Candida albicans* and *Escherichia coli* was described [85].

**Protease inhibitors**

Paronychia, ingrowing nails, pyogenic granulomas, and onycholysis of the great toes appeared in 42 AIDS patients receiving multiple antiretroviral therapies. In all patients the nail lesions developed after the introduction of the protease inhibitor [86, 87].

Single case reports of paronychia during therapy with protease inhibitors include ritonavir-boosted lopinavir in a 25-year-old woman receiving aripiprazole for schizophrenia [88], nelfinavir [89], and indinavir [90, 91].

Darkening of fingernails and toenails was seen during treatment with indinavir, ritonavir, abacavir, and lamivudine [92].

**Antifungal drugs**

**Itraconazole**

Treatment with itraconazole has been described as responsible for an increase in the nail growth rate. This may be due to the antioxidant effects of itraconazole and its metabolite hydroxyl-itraconazole [93]. This acceleration of nail growth has been associated with the occurrence of longitudinal banding of the nail plate [94]. Some authors have used this property of itraconazole to treat patients with yellow nail syndrome [95].

Evident onychodermal bands of the toenails were reported in a patient treated with itraconazole for onychomycosis [96].

**Fluconazole**

Accelerated nail growth has been reported after treatment with fluconazole [97]. For this reason, fluconazole has been used in the treatment of yellow nail syndrome in combination with vitamin E [98].

Longitudinal melanonychia has been associated with fluconazole therapy in one patient: the pigmentation appeared after 1 month of treatment and remained 3 months after cessation [99].

**Ketoconazole**

Splinter hemorrhages and longitudinal pigmented bands have been described in patients taking ketoconazole [100].

**Amorolfin**

In patients who erroneously applied amorolfin 5% nail lacquer on a daily rather than a weekly basis, bluish or yellow-brown nail discoloration has been reported. This pigmentation does not occur in all cases and is probably due to oxidation of one of the constituents of the formulation [101].

The term “lacquer nail” has been coined to describe a nail plate abnormality caused by overzealous filing of the nail during treatment of onychomycosis with antifungals in nail lacquers: distal thinning and fragility of the nail plate and nail bed erythema are associated with signs of onychomycosis (Fig. 16.10) [102].

![Figure 16.9](image)

**Figure 16.9** Zidovudine-induced nail pigmentation.

![Figure 16.10](image)

**Figure 16.10** "Lacquer nail": nail plate shortening and distal thinning with fissuring due to excessive filing.
Allergic contact dermatitis to amorolfine contained in the nail lacquer manifests itself as a pruritic erythematous rash on the dorsum of the treated digit that regresses after interruption of the lacquer application [103].

**Ciclopirox (ciclopirox olamine)**

The antifungal agent ciclopirox is marketed in lacquers for treatment of onychomycosis with two different vehicles: 8% ciclopirox in polyvinyl nail lacquer (water-insoluble resin), and 8% ciclopirox in hydroxypropyl chitosan-based, water-soluble nail lacquer. Both topicals may rarely induce mild erythema and burning of the periungual tissues, which seem more common with the polyvinyl nail lacquer and are probably due to its inactive ingredients and not to ciclopirox itself [104]. Although some cases of allergic contact dermatitis to ciclopirox in cream [105] or milk [106] have been reported in the literature, no cases of allergic contact dermatitis due to ciclopirox in nail lacquer have been reported so far.

The use of ciclopirox in water-insoluble nail lacquer can be associated with the development of “lacquer nail,” if the nail filing that is indicated once a week during treatment is excessively performed [102]. Ciclopirox in water-soluble nail lacquer does not need weekly use on nail polish, as the lacquer is removed by water. An asymptomatic reversible whitish discoloration of the nail, due to stratification of the product, can sometimes occur (Fig. 16.11).

**Voriconazole**

Nail changes and nail loss were reported respectively by 106 (70%) and 15 (10%) of 152 patients who received voriconazole for at least 1 month for probable or confirmed fungal infection. Nail changes were more common in patients experiencing voriconazole-induced hair loss and consisted of nail fragility, splitting, and brittleness [107].

**Antimalarial agents**

As chloroquine is accumulated in the nails over a long period, measurement of chloroquine in toenail samples can be useful in assessing drug intake dating back to at least 1 year [3].

The occurrence of pigmentary changes is a characteristic side-effect of antimalarial therapy. A study on 209 antimalarial users reported hyperpigmentation in 33% of patients, with no relationship to the patient's ethnic background, age, gender, or type of antimalarial used [108]. The pigmentation involves the dermis of the nail bed and can be bluish-black or bluish-brown in color, diffuse or in transverse bands [109–111] (Fig. 16.12). Regarding pathogenesis, the nature of the pigment is still unknown but both melanin and hemosiderin deposits appear to be present. The presence of a complex containing the antimalarial has also been suggested [112]. Several months are needed to observe the decrease in nail pigmentation after cessation of therapy and sometimes pigmentation may not disappear completely.

Nail discoloration varying from white, diffuse yellow or lemon-green, to blue-green or gray has been described in patients taking mepacrine [59]. A characteristic green-yellow or whitish fluorescence of the nails is commonly observed under Wood's light. Nail pitting, ridging, and shedding can also occur during mepacrine treatment.

Antimalarial agents may induce or exacerbate psoriasis. Sibilia et al. described a case of psoriatic onychoperiostitis precipitated by hydroxychloroquine [113].

![Figure 16.11 Whitish discoloration of the nails caused by ciclopirox.](image1)

![Figure 16.12 Antimalarial-induced diffuse nail pigmentation. Courtesy of J.L. Verret.](image2)
Photodistributed lichenoid drug eruption induced by antimalarials (quinine, hydroxychloroquine) may involve the nail with photoonycholysis [114] or erosive plaques affecting the dorsal aspects of the fingers and the majority of nail folds [115].

Drugs acting on the central nervous system

Anticonvulsant drugs

Onychomadesis has been described as a side-effect of carbamazepine [116–118]. Drug discontinuation is followed by return to normal nails.

Onychomadesis has also been reported in a child undergoing sodium valproate therapy [119–121]. Other reversible nail changes associated with sodium valproate therapy and not related to its dose include onycholysis of one or all nails [121–123], yellow discoloration, and nail plate roughness [123, 124].

Phenytoin has been reported as responsible for an acute lichen planus-like eruption with nail involvement (Hancke, unpublished).

Regitabine (ezogabine) intake induces a progressive blue pigmentation of face, lips, hard palate, conjunctiva, and nail, due to melanin dermal deposition. All 20 nails show transverse or total blue discoloration [125, 126]. Pigmentation slowly fades after drug discontinuation.

Benzodiazepines

Clorazepate dipotassium induced photoonycholysis and subungual hemorrhages in one patient [127].

Tricyclic antidepressants

Longitudinal leukonychia has been reported in patients treated with trazodone hydrochloride [128, 129].

Venlafaxine

Subungual hyperkeratosis and palmoplantar keratoderma have been described in a patient during venlafaxine treatment for a depressive disorder [130].

Phenothiazines

Pigmentation on exposed areas of skin has been observed in patients taking high doses of chlorpromazine and related phenothiazines for prolonged periods. This pigmentation ranges from tan or slate blue to a deep blue-black or purple color. In severe cases, the nail beds are also involved [131]. This pigmentation is cumulative, increases during summer months, and fades slightly in winter.

Photoonycholysis was rarely reported with phenothiazines.

Lithium carbonate

A rich golden color of the distal nail plate has been described with lithium therapy [132]. Transverse brown-black pigmented bands followed by latent onychomadesis have also been observed [133].

Precipitation or worsening of psoriasis by lithium treatment is well known: a case of psoriatic trachonychia of the fingernails has been observed as the sole manifestation of lithium ingestion [134] (Fig. 16.13).

A unique case of Darier disease induced by oral lithium has been reported [135].

Buspirone

Nail thinning has been described as a consequence of buspirone treatment.

L-dopa

In patients taking L-dopa therapy for Parkinson disease, accelerated nail growth and increased hardness of the nail have been reported [136].

Rotigotine

Reversible green dyschromia involving the fingernails bilaterally appeared a few days after starting rotigotine, a non-ergot dopamine agonist used in Parkinson disease [137].

Clomipramine

A band-like brownish discoloration appeared in a patient on clomipramine therapy [138].

Methylphenidate

A 6-year-old boy developed an episode of nail biting causing bleeding and nail damage approximately 1 h after
taking a 20 mg dose of methylphenidate for attention deficit hyperactivity disorder [139].

**Cocaine**

Parrot beak nails, i.e. claw-like nails due to nail plate longitudinal hypercurvature and atrophy of the distal pulp, are a common finding in young females who use crack cocaine [140–142]. They are associated with pernio and hyperkeratosis of the knuckles and result from peripheral ischemia due to vasoconstriction induced by cocaine.

Livedo reticularis, acrocyanosis, generalized myalgias, and proximal muscle weakness with periungual erythema, microinfarctions, and diffuse swelling have been observed in a 20-year-old female after the inhalation of cocaine in a base pipe [143].

Long fingernail growth (usually the fifth) has been described in users of personal cook spoons. Burns on the fingertips of the first and second digits on the dominant hand can occur during use of a crack pipe [144].

**Antiinflammatory agents**

**Aspirin, acetylsalicylic acid (ASA)**

Purpura of the nail bed can be seen in patients taking aspirin.

**Benoxaprofen**

Benoxaprofen has been withdrawn from the market because of its serious side-effects. Photoonycholysis was a common side-effect and was possibly related to the ability of the drug to stimulate spontaneous oxidative metabolism and degranulation of human leukocytes [145, 146]. Onycholysis without photoonycholysis was observed in toes [147].

Accelerated nail growth [148, 149] and koilonychia have also been described.

**Ibuprofen**

Longitudinal melanonychia has been reported during ibuprofen therapy.

**Phenazopyridine**

Deep lemon-yellow discoloration of the nails has been reported in a patient taking phenazopyridine 300 mg/day for more than 3 years [150].

**Salsalate**

Lichenoid eruption with longitudinal onychoschizia and onychomadesis have been described in a 92-year-old man after starting treatment with salsalate for arthritic pain [151].

**Cardiovascular drugs**

**Beta-blockers**

Beta-blockers have been implicated in psoriasiform skin eruptions and the exacerbation of preexisting psoriasis [152]. Psoriatic fingernail changes were observed in the digits utilized to hold down the eyelid during application of an eye drop containing timolol [153]. The nail alterations resolved after eye drop discontinuation. Reversible pincer nails appeared in a 48-year-old woman treated with practolol: painful narrowing of the nail bed and excessive transverse overcurvature were associated with subungual hyperkeratosis, onycholysis, and brownish discoloration of the nail plate [154]. Onycholysis and nail discoloration have been described during propranolol treatment (Fig. 16.14). Tiny periungual pustules have also been seen [155]. Nail changes typical of psoriasis unresponsive to topical and systemic treatments developed in a patient undergoing metoprolol treatment. Psoriasiform abnormalities resolved completely with the withdrawal of the drug and recurred with drug rechallenge [156, 157].

Beau’s lines and alopecia have been reported during metoprolol treatment [158].

Cold extremities and Raynaud phenomenon are classic side-effects of beta-blocker treatment. Pterygium inversum unguis can also occur. Peripheral ischemia with digital gangrene is a rare complication of beta-blocker treatment that almost exclusively occurs in patients treated for hypertension. Although every type of beta-blocker can cause digital necrosis, propranolol is more commonly responsible [159, 160]. Since improvement of symptoms does not always follow withdrawal of the drug, digital or limb amputation has been the final outcome in several patients.

A patient with pheochromocytoma experienced acral skin necrosis with splinter hemorrhages and periungual telangiectasias after taking atenolol. The skin biopsy showed epidermal and sweat gland necrosis [161].

**Figure 16.14** Psoriasiform nail changes during propranolol treatment.
Reversible symmetrical brown discoloration of nearly all the nails of the fingers and toes has been reported in a 56-year-old woman affected by glaucoma and treated with timolol maleate 0.5% eye drops [162]. These changes developed slowly and spread on the nails in different intensities.

**Amiodarone**

Some nail abnormalities have been described in patients with hypothyroidism secondary to amiodarone treatment [163].

**Angiotensin-converting enzyme inhibitors**

The antihypertensive drugs captopril and enalapril have been implicated in nail abnormalities [164]. In patients treated with captopril, reversible onycholysis has been reported [165], as has a lichenoid skin eruption associated with lichenoid nail dystrophy [166] (Fig. 16.15).

**Clonidine**

Raynaud syndrome is a possible side-effect of clonidine treatment.

**Calcium channel blockers**

New-onset psoriasis as well as exacerbations of it are common side-effects of several calcium channel blockers, including diltiazem, nifedipine, felodipine, and amlodipine [167].

A case of pemphigoid nodularis with involvement of face, scalp, trunk, limb, and several nails was reported during nifedipine treatment. Nail lesions progressed to dorsal pterygium [168].

Longitudinal melanonychia and periungual pigmentation of several fingernails and toenails have been noted in a 75-year-old man receiving amlodipine for hypertension [169].

**Angiotensin II receptor blockers**

Clubbing, onycholysis, and yellow-brown discoloration of the distal nails were reported in a 76-year-old man receiving losartan and then valsartan for hypertension [170]. Nail changes regressed when the sartan was replaced by captopril.

Sartans may be responsible for lichenoid drug eruption involving the nails [171].

**Quinidine**

Horizontal blue-gray discoloration of the nail bed has been described in an 83-year-old man receiving quinidine [172].

**Amrinone**

One of 18 patients reported by a case series on side-effects of amrinone developed bright yellow nail discoloration that disappeared after drug withdrawal [173].

**Anticoagulant drugs**

Subungual hematoma can be observed during anticoagulation, especially in the toes (Fig. 16.16) [174]. In patients submitted to long-term treatment with phenindione intermittent diffuse, orange-colored staining of the fingernails has also been observed.

Diffuse brown-black pigmentation of all nails, more prominent on the lateral side of the nail, was reported in a woman undergoing treatment with the low molecular weight heparin tinzaparin sodium [175]. The patient's nails returned to normal 6 months after discontinuation of therapy.

Heparin treatment can reduce nail growth rate.
Warfarin

The purple toes syndrome has been described as a rare ischemic complication of oral anticoagulants. It includes painful purple discoloration of the toes and sides of the feet. The discoloration develops 3–8 weeks after the beginning of therapy and fades usually on moderate pressure or with leg elevation [176]. Although pathogenesis is still debated, pathological studies suggest that the purple toes are a consequence of cholesterol microembolization. Purple toes syndrome may herald diffuse arterial obstruction by microembolic disease.

Hormones

Oral contraceptive pill

An increased growth rate of nails and reduced splitting and “chipping” have been reported in some postmenopausal women taking the oral contraceptive pill [177]. Photoonycholysis due to porphyria cutanea tarda may occur in patients taking the oral contraceptive pill [178]. Nail shedding has also been observed following oral contraceptive treatment.

Androgens

A clinical picture resembling half-and-half nails has been described in a breast cancer patient after androgen therapy [179].

Parathyroid extracts

Onychomadesis has been reported with parathyroid extract medication [180].

Corticosteroids

Nail side-effects may be observed after prolonged topical application or intralesional administration of steroids for treating different nail diseases.

The frequent application of potent local steroids, even without occlusion, induces skin atrophy that may involve the distal phalangeal bone in the so-called “disappearing digit” [181]. Atrophic tapering of the fingertip may occur as soon as after only 1 month of treatment, with the finger looking like a sharpened pencil (Fig. 16.17) [182]. Striking atrophy of the terminal phalanges of the fingers was noted in both hands in one case [183]. Severe thinning, erythema, and scaling were noted in affected areas. The nails exhibited diffuse yellow discoloration and subungual hyperkeratosis whereas the nails of both thumbs were lost. After discontinuing corticosteroid treatment, 2 years are needed to recover normal appearance of the hands but there may still be slight persistence of some degree of acroatrophy.

Intralesional steroids are commonly used in the treatment of nail psoriasis and lichen planus. Side-effects include hypopigmentation (Fig. 16.18) [184] and intramatrical hemorrhages which appear later below the nail plate. Permanent damage of the nail matrix may result from injections given too frequently or in too concentrated a dosage.

The occurrence of multiple implantation epidermoid cysts in a patient with psoriasis treated with steroids by Dermojet is now well known. It necessitated the amputation of some of the distal phalanges (J. Mascaro, personal communication).

A single band of transverse leukonychia in all fingernails and toenails has been reported in a white woman after cortisone administration [185].
Transverse melanonychia due to prednisone has also been described by Thomsen (personal communication).

**Adrenocorticotropic hormone, melanocyte-stimulating hormone**

Transverse melanonychia has been described in patients taking adrenocorticotropic hormone (ACTH), melanocyte-stimulating hormone (MSH), or synthetic alpha-melanocyte stimulating hormone (alpha-MSH) [186]. Melanonychia is reversible after interruption of the drug and is due to transient synthesis of melanin by nail matrix melanocytes, as Fontana stain reveals melanin in nail plate onychocytes.

**Levothyroxine sodium**

A patient undergoing levothyroxine treatment developed periungual and subungual pyogenic granulomas of several nails [187]. The pathogenesis of this side-effect may reside in the proangiogenic and proliferative effects of levothyroxine.

**Propylthiouracil**

Lichenoid eruption with reddish nodules on nail beds and fingernail dystrophies has been described in a 42-year-old woman receiving propylthiouracil for hyperthyroidism [188].

**Cancer chemotherapeutic agents**

See Chapter 17.

**Miscellaneous**

**Ascorbic acid**

Exogenous nail pigmentation appearing as a yellow discoloration of fingernails and toenails, sparing the proximal side of the nails, was seen in a 74-year-old man who had been applying a galenic topical preparation containing ascorbic acid 1% on all nails for 3 months to “prevent onychomycosis” [189].

**Carotene**

Long-term treatment with carotene can produce yellow discoloration of the nails.

**Ciclosporin (cyclosporine)**

Raynaud phenomenon has been reported in two patients 2 days after treatment with ciclosporin (10 mg/kg/day) was started. A relapse was noted with reintroduction of the drug (5 mg/kg/day) in one patient. An increase of linear nail growth was noticed by Baran (personal observation).

Periungual pyogenic granulomas, sometimes appearing as repeated ingrowing toenails that did not recur when ciclosporin was stopped, have been described by several authors [190–192]. A 39-year-old woman who had undergone renal transplantation developed acquired digital fibrokeratoma while receiving ciclosporin [193]. Marked pitting and single homogeneous transverse white lines were described extending across the entire width on all the fingernail plates of a 41-year-old man treated with ciclosporin for psoriasis. These lesions were not present before treatment began [194].

**Dandelion tea**

A patient with end-stage renal disease developed necrosis of the distal phalanges of both thumbs and the lateral three digits of both hands due to secondary hyperoxalemia and deposition of oxalate crystals in tissues [195]. The source of oxalate was dandelion tea, which the patient had been drinking in high quantity (10–15 cups daily) for 6 months. Hyperoxalemia resulted from high dietary oxalate associated with reduced renal clearance.

**Dimercaptosuccinic acid**

A 16-year-old boy developed longitudinal striations on the base of his nails after dimercaptosuccinic acid (DMSA) administration [196].

**Diuretics**

Thiazide diuretics have been implicated in some cases of onycholysis, and indapamide was reported to induce photoonycholysis [36].

**Herbal medicines**

A 48-year-old woman noted that her fingernails stopped growing for 7 years after self-administration of podophyllotoxin for chronic headaches [197].

**Hydroquinone**

A reversible brown or orange-brown pigmentation of the nails can be observed in persons who apply topical hydroquinone on face or hands [198, 199]. The exogenous pigmentation usually involves the distal part of the fingernails and may become more intense after sun exposure [200].
Interferon alfa

Longitudinal melanonychia of several nails was reported in 9% of 77 patients undergoing interferon alfa treatment for chronic hepatitis C virus infection [201] (Fig. 16.19). It was often associated with oral mucosa hyperpigmentation.

Raynaud phenomenon followed by finger- and toenail necrosis resulting in digit amputation was reported in two patients during treatment with interferon alfa [202].

Interferon beta

Three patients developed hyperpigmented nail beds associated with sclerosing skin disorders during treatment for multiple sclerosis [203].

Pamidronic acid

A 52-year-old woman developed pincer nails following a single infusion of pamidronic acid for osteomalacia [204].

Peloprenoic acid

Nail fragility was observed in patients with psoriasis treated with peloprenoic acid derivatives (Ohkido, personal communication).

Penicillamine and bucillamine

Absence of the lunulae, longitudinal ridging, onychoschizia, elkonyxis, and Beau’s lines have been reported after penicillamine treatment [205]. Nail matrix anomalies, deep longitudinal grooves with leukonychia, striations, and distal onychoschizia can also be seen [206, 207]. Nail changes are reversible after cessation of treatment.

Yellow nail syndrome has been described in several patients following penicillamine or bucillamine treatment for rheumatoid arthritis [208–213]. The complete triad of yellow nails, lymphedema, and respiratory disease can be present, as well as nail signs only. A recent review of the Japanese literature on bucillamine-induced yellow nail syndrome found time of onset of the yellow nail syndrome to be a median of 17 months after beginning therapy. Ninety per cent of the cases showed improvement of the yellow nail after bucillamine discontinuation, while improvement of pulmonary disease and lymphedema was observed in a smaller percentage of patients [214].

Phenylephrine

Purpura of the nail bed has been reported [99].

Psoralens

Photoonycholysis can be observed in patients undergoing psoralen ultraviolet A (PUVA) therapy (Fig. 16.20) [215–217] or in those treated with sunlight and oral psoralen.

Pulse oximetry

Hematoma of the proximal nail fold can occur after oximeter use during anesthesia and monitoring of critically ill patients. The hematoma affects the distal part and spares the cuticle, and its occurrence is not necessarily related to prolonged use of the oximeter [218, 219].
Digital skin necrosis is a more severe complication of pulse oximetry [220]. Cyanosis and bullae formation may be seen in less severe cases. Lesions are probably due to pressure necrosis and occur at the site of application of the probe sensor. The pediatric population is more predisposed to such injuries [221–223].

Oximeter readings of oxygen saturation value may be altered in patients with excessively long nails [224], in nails with nail polish [225], and in acrylic nails [226].

Purgatives

Reversible finger clubbing has been noted in purgative abuse [227–229].

A bluish discoloration of the lunulae can be observed in patients treated with phenolphthalein [230]. Paronychia and nail plate ridging have also been reported.

Radiation

UVB and UVA phototherapy may induce longitudinal melanonychia and photoonycholysis. In a case report, one finger developed a subungual melanoma and a second finger was affected by benign melanocytic hyperplasia [231].

Onychomadesis, Beau's lines, and melanonychia can be seen following radiation therapy [232].

Both transverse and longitudinal melanonychia of several nails have been reported in patients treated with total skin electron beam therapy for mycosis fungoides [233, 234].

Retinoids

Synthetic retinoids have evident effects on nail keratinization (Fig. 16.21). Most of the side-effects induced by retinoids on the nail apparatus are dose related and can be explained as part of the general desquamative process. The delay in the appearance of nail complications ranges from 2 weeks to 18 months after the commencement of therapy. Their occurrence is unpredictable but the changes are far more frequent in patients with psoriasis than in other subjects. Sometimes the nail changes are transient even when medication is continued [235–237]. Linear nail growth may be normal or more frequently decreased [238]. Accelerated fingernail growth has, however, been documented in patients with psoriasis [239].

Nail thinning, splitting, softening, and fragility are commonly seen during etretinate treatment [240]. A nail biopsy obtained from a patient who developed softening, thinning, and depression of the proximal nail plate showed inadequate keratinization of the nail plate in the absence of inflammatory changes [240]. Although thinning of the nails can be regarded as a positive result in patients with thick psoriatic nails, some patients complain of increased sensitivity to external pressure and inability to use the nails in a functional way. Beau's lines, latent or complete onychomadesis, proximal onychoschizia, and transverse leukonychia are other possible consequences of nail matrix damage [237, 241–244].

Progressive onychatrophy may lead to nail loss [245, 246]. Onycholysis is an uncommon complication of etretinate therapy and even rarer with isotretinoin [237, 246, 247]. Elkonyxis has also been reported [248]. Elkonyxis has also been reported in a 53-year-old woman during treatment with isotretinoin for rosacea [249]. Bilateral fragility and onycholysis were reported as well [250]. A 35-year-old woman treated with etretinate 0.25 mg/kg/day developed distal hemitorsion of the nail plates of several fingernails. This unusual side-effect of etretinate has been referred to as "curly nails" [251].

Median nail dystrophy has been associated both with isotretinoin and altretinoin therapy, although the real role of retinoids in the pathogenesis of this auto-induced nail change is possibly only that of increasing nail fragility [252–255].

Chronic paronychia originating from periungual psoriatic foci frequently occurs in patients with psoriasis treated with etretinate related to retention of scales on the undersurface of the proximal nail fold [237] (Fig. 16.22). Pyogenic granuloma-like lesions of the nail folds may be associated with chronic paronychia or may occur separately [256]. Increased skin fragility along with nail plate brittleness resulting in fine spicules that break through the lateral nail grooves are possibly responsible for this peculiar side-effect [237]. Pyogenic granuloma-like lesions can also occur during isotretinoin treatment [257, 258], and have also been reported with topical application of tazarotene [259] (Fig. 16.23). Ingrowing nails can occasionally be observed (Fig. 16.24).
Figure 16.21 Nail changes due to etretinate. (a) Transverse leukonychia. (b) Proximal onychoschizia. (c) Fingertip peeling and onycholysis. (d) Nail shedding. (e) Paronychia associated with pyogenic granuloma. Courtesy of H. Zaun. (f) Pyogenic granuloma. Courtesy of J. Delescluses.
Recurrent subungual hemorrhages of one finger were reported in a patient undergoing acitretin treatment for palmoplantar keratoderma due to psoriasis [260]. Nail dystrophy and brittle nails have been described with vitamin A treatment [261].

**Salbutamol**

Salbutamol has been implicated in causing periungual and palmoplantar erythema in a pregnant woman [262].

**Sirolimus**

A study on 80 patients receiving sirolimus after renal transplantation revealed nail abnormalities in 74% of the cases [263]. All constituents of the nail apparatus and nail bed blood vessels were damaged by the drug, possibly through inhibition of the EGF pathway. Signs of matrix damage were the most common, including slow nail growth, fragility, onychorrhexis, and true leukonychia. Other reported nail changes were onycholysis, splinter hemorrhages, and periungual pyogenic granulomas. One patient developed photoonycholysis.
Tiopronin

Reversible yellow nail syndrome, characterized by nail changes, lymphedema, and pleural effusion, has been associated with treatment with tiopronin, a thiol compound utilized in the treatment of rheumatoid arthritis [212, 213].

Intoxicants

Toxic oil syndrome

In 1981, 20,000 people in Spain ingested an oil fraudulently sold as olive oil and suffered from a previously unrecorded condition, later known as toxic oil syndrome (TOS), clinically characterized by intense incapacitating myalgias, marked peripheral eosinophilia, and pulmonary infiltrates. During the chronic phase of the disease, Raynaud phenomenon and scleroderma-like changes were observed in 9–13% of the cases [264].

Polychlorinated biphenyl intoxication

Dark-brown pigmentation of the fingernails and toenails has been reported in workers exposed to polychlorinated biphenyl (PCB). Nail deformities were described in 68% of patients with PCB poisoning due to the consumption of rice-bran cooking oil contaminated by large amounts of PCBs and congeners. Flattened nails were noted in 25% of patients [265, 266]; ingrowing nails and lamellar dystrophy were also common.

One third of the children born from a few months to several years after maternal PCB poisoning showed nail changes, including koilonychia, transverse grooves, ridging, thinning, longitudinal splitting, onychauxis, and transverse overcurvature. Hyperpigmentation of the nail plate and bed was also observed. Toenails were affected more often than fingernails [267, 268].

Carbon monoxide intoxication

Cherry red discoloration of the nail bed is a symptom of carbon monoxide intoxication [269]. A case of mild onycholysis of two fingernails without color changes following carbon monoxide exposure has been reported [270]. Carbon monoxide poisoning is followed by superficial necrosis of the distal phalanges involving pulp and periungual region, ears, and nose [271].

Selenium intoxication

Selenium intoxication usually results from ingestion of misformulated dietary supplements that contain hundred times the labeled concentration of selenium, or after ingestion of nuts of *Lecythis ollaria* (paradise nuts) or other selenium-accumulating plants. Several outbreaks have been reported, with nail signs as common features [272–279]. These included white to gray transverse streaks, yellow discoloration, nail brittleness, onycholysis and fingertip tenderness, swelling, and purulent discharge.

Vinyl chloride exposure

Raynaud phenomenon, associated or not with proximal nail fold capillary abnormalities, may be a long-term sequela of occupational exposure to vinyl chloride [280]. Scleroderma-like changes and acroosteolysis have also been reported, as have clubbing-like nail changes in the fingers [281].

*Dieffenbachia seguine*

Fingertip necrosis of the right thumb has been reported in a patient after contact with *Dieffenbachia* guttation fluid [282]. The fluid penetrated through a skin rhagade and its poisonous metalloproteinase induced massive skin necrosis with osteolysis. Immediate debridement was necessary to stop disease progress.

Heavy metal intoxications

Arsenic

Many assays can be used to detect arsenic in body tissues, hair, and nails, including colorimetry, polarography, X-ray fluorescence, atomic absorption, and neutron activation analysis. Nail samples containing more than 3 μg/g arsenic are positive for arsenic intoxication. Chronic arsenic toxicity occurs primarily through inadvertent ingestion of contaminated water and food or occupational exposure, but it can also occur through medicinal ingestion [283].

Mees’ lines are a typical sign of arsenic poisoning [284, 285]. They appear as transverse white bands of true leukonychia that move distally with nail growth (Fig. 16.25). A single broad band is usually seen but multiple lines are sometimes observed. These bands typically appear 4–6 weeks following an acute episode of arsenic poisoning.

Other nail changes described in arsenic poisoning include Beau's lines, onychomadesis, longitudinal brown hyperpigmented bands, and a diffuse blackish-brown discoloration of the nail plate.

Black foot disease describes an endemic peripheral vascular disorder resembling Buerger disease that occurred in a limited area of southern Taiwan [286]. The term described the foot color that resulted from gangrene of the extremities due to drinking artesian well water containing both arsenic and chemically unknown fluorescent substances.
Bluish-black pigmentation of the skin of sun-exposed areas, including the periungual regions, is an essential feature of argyria [287]. The nails may present a diffuse silver-gray discoloration (Fig. 16.26) or a slate-blue coloration on the proximal nail bed, more evident on the lunulae (Fig. 16.27). The toes are usually not involved. Isolated chromonychia of the fingernails in the absence of skin pigmentation has also been described [288]. The degree of discoloration parallels the amount of dermal iron deposits and is most prominent in sun-exposed areas, as the silver compounds upregulate melanin production, and sunlight catalyzes the reduction of the colorless silver compounds in the dermis to elemental silver, which is then oxidized and bound to form the metallic silver sulfide [289]. Histopathology reveals deposition of silver granules in the dermal tissue both in light-exposed skin and non-exposed areas [290]. The pigmentation is permanent.
Mercury

Acrodynia is a rare disorder occurring in infancy due to chronic exposure to mercury. Excruciating pain in the hands and feet associated with intermittent pink staining of the tips of the fingers, toes, and nose is an early manifestation of the disease [291]. Ridging, fragility, and dark discoloration of the nail plates are commonly observed. Alopecia and nail loss have been reported in severe cases. Gangrene of the extremities may develop [292]. Oral treatment with 2,3-dimercaptosuccinic acid (DMSA) can be utilized as chelation therapy. Alternatives are hemodialysis, peritoneal dialysis, and plasma exchange [293].

After chronic exposure to topical preparations containing mercury, a grayish-brown nail discoloration can occur [294]. Hair loss and brown pigmentation of the distal portion of the fingernails have been observed in a patient with chronic mercury poisoning caused by the use of mercury-containing cosmetic bleaches. The mercury content of the patient’s nails was extremely high [295]. A similar case has also been reported by Bockers et al. [296].

Some cases of systemic lichen planus with nail involvement due to mercury in dental amalgam have been reported [297, 298].

Gold

Chrysotherapy describes the treatment of rheumatoid arthritis patients with monovalent gold drugs possessing antiinflammatory and other properties. Nail side-effects include yellow to dark brown nail plate pigmentation, slowed nail growth, and nail thickening as well as nail thinning and permanent onycholysis [299–302]. There is no correlation between gold levels in skin, hair, and nails and gold toxicity [303].

Lead

Diffuse hyperpigmentation of the fingernails and toenails occurred in a 55-day-old boy using an astringent powder with a high lead content [304]. Partial leukonychia, nail bed hyperkeratosis, and onychomadesis have also been reported.

Thallium

Several nail changes have been described in thallium poisoning, including diffuse or partial brownish nail discoloration, onychorrhexis, and transverse leukonychia [305]. Onychomadesis occurred in 73% of 26 persons after acute thallium intoxication [306].

Dry scaling of the distal parts of the extremities can also be seen [307].

Aniline

A purplish blue discoloration of the nail bed due to cyanosis is a typical finding of aniline poisoning [308].

Chromium salts

Dichromates produce a yellow ocher color of the nails [308].

Fluorine

Changes in the skin and its appendages including teeth, nails, and hair have been noticed after prolonged fluoride ingestion. Various nail dystrophies occur including brittleness, onychorrhexis, Beau’s lines, pitting, and punctuate and transverse leukonychia producing “mottled” nails of both fingers and toes [309, 310].

Iron

Exogenous brown discoloration of all nails and hair has been reported after the use of water with a high iron content [311].

References

Drug‐induced Nail Disorders


Drug‐induced Nail Disorders


Drug-induced Nail Disorders


Drug-induced Nail Disorders


Chapter 17

Anticancer Therapies

Vincent Sibaud¹, Robert Baran², Bianca Maria Piraccini³, Mario E. Lacouture⁴, and Caroline Robert⁵,⁶

¹ Department of Oncodermatology, Institut Universitaire du Cancer – Toulouse Oncopole, Toulouse, France
² Hon. Pr. of the University of Franche-Comté; Nail Disease Centre, Cannes, France
³ Dermatology, Department of Experimental, Diagnostic and Specialty Medicine, University of Bologna, Bologna, Italy
⁴ Dermatology Service, Memorial Sloan Kettering Cancer Center, New York, NY, USA
⁵ Department of Dermatology, Institut Gustave Roussy, Villejuif, France
⁶ Department of Dermatology, Paris-Sud University, Orsay, France

Chemotherapy and targeted therapies

Nail changes represent one of the most common toxicities in patients treated with systemic anticancer treatments. These nail toxic effects can involve different components of the nail apparatus, including the nail bed (onycholysis, apparent leukonychia, splinter hemorrhages), the nail matrix (Beau’s lines, onychomadesis, true leukonychia, slower nail growth, nail thinning, brittle nails, melanonychia), and the perionychium (paronychia, pyogenic granuloma) [1–3]. Patients commonly present a combination of nail changes, which may affect all or some nails (Fig. 17.1). Because of the specific kinetics of nail formation and growth, it is important to note that the occurrence of these nail toxic effects is often delayed relative to treatment initiation. Most nail changes observed in this context are usually transitory, well-tolerated, disappear with drug withdrawal, and may only represent a cosmetic issue. Hence education and reassurance are important (Box 17.1). Some nail toxic effects, however, can be very painful or functionally debilitating [4] and may require proactive management, e.g. taxane-related onycholysis or anti-epidermal growth factor receptor (EGFR)-related pyogenic granuloma. Therefore, nail toxicities may represent one of the most burdensome adverse events in cancer patients [5].

Cytotoxic chemotherapeutic agents mainly induce toxic effects on the nail bed and the nail matrix. By contrast, periongual lesions are the most frequent and the most debilitating nail-related adverse events reported with targeted anticancer therapies [1].

Nail changes induced by chemotherapy

Most frequent nail changes

Beau’s lines and onychomadesis

Beau’s lines correspond to the formation of transverse linear depressions in the dorsum of the nail plate and result from a transitory decrease in mitotic activity of the proximal nail matrix keratinocytes. The depth of the groove is strictly correlated to the extent of nail matrix damage. The width is proportional to the duration of the insult. Beau’s lines have been described with nearly all chemotherapeutic agents, especially when used in combination or with a high-dose regimen. They are probably the most frequent nail changes noted in patients exposed to chemotherapy [1–3]. Beau’s lines often affect all nails but are more frequent in fingernails (Figs 17.1, 17.2). After repeated
courses of chemotherapy, several depressions can be noted in the same nail. They move distally with nail growth. Beau’s lines may evolve into the formation of onychomadesis, which corresponds to the extreme form of Beau’s lines (Fig. 17.3). The nail plate is then divided into two parts by a transverse thick groove [6], which remains latent for a long period before the nail plate ultimately sheds.

Figure 17.1 Combination of nail changes with chemotherapy (onycholysis, onychoschizia, melanonychia, leukonychia, and Beau’s lines).

Box 17.1 Counseling for prevention of nail toxic effects (both with targeted therapies and chemotherapy)

- Provide the patient with clear and detailed information.
- Avoid repeated trauma or friction and pressure on nails and nail beds (manicuring, artificial nails, nail biting, removal of the cuticle, etc.).
- Use protective gloves (cotton, rubber).
- Avoid prolonged contact with water (e.g. dishwashing), detergents.
- Restrict use of nail polish removers and hardeners.
- Trim nails regularly – ensure that they are straight/squared and not too short. Smooth the edges.
- Apply topical emollients daily (cuticles, plate, and periungual folds) and nail lacquers (to limit water loss from the nail plate).
- Wear comfortable wide-fitting footwear and cotton socks – visit a podiatrist if needed.
- For brittle nails use FDA-approved nail lacquers (hydroxypropyl chitosan, polyurethane 16%) ± oral biotin.
- Obtain bacterial/viral/fungal cultures if infection is suspected.

Figure 17.2 Diffuse onycholysis (docetaxel) associated with Beau’s lines.

Figure 17.3 Onycholysis combined with Beau’s lines and onychomadesis (paclitaxel).
Melanonychia

Melanonychia also represents one of the most common nail changes with chemotherapy [1–3, 7–9]. A wide range of antineoplastic drugs can induce melanonychia: hydroxyurea, busulfan, doxorubicin, fluorouracil and its prodrug capecitabine, taxanes, bleomycin, cyclophosphamide, cisplatin, etc. Melanonychia develops after 1–2 months of treatment. Several nail plates can be simultaneously affected (Figs 17.1, 17.4, 17.5). Skin or mucosal pigmenitary changes are frequently associated.

Melanonychia results from direct toxic action of chemotherapy on the melanocytes of the nail matrix, with secondary melanin production analogous to the postinflammatory hyperpigmentation seen in skin. The activation of a subgroup of melanocytes produces a single or several longitudinal pigmented bands (melanonychia striata) whereas diffuse activation of melanocytes gives rise to total melanonychia. Transverse melanonychia may also be observed.

Chemo-induced hyperpigmentation does not require any treatment and progressively regresses several months after treatment discontinuation. For patients who would like to conceal this melanonychia, dark-colored nail polish may be proposed.

Leukonychia

Leukonychia may also occur [1–3, 10–12], but less frequently and mainly in the form of apparent leukonychia. Apparent leukonychia (white transparent coloration) results from changes in blood flow in the nail bed and does not move with nail growth. It can present as three different clinical types: Muehrcke’s lines (the most frequent form in association with chemotherapy), half-and-half nail, or Terry’s nails (Fig. 17.5). True leukonychia (total or transverse – Mees’ lines – white opaque coloration) due to the impairment of keratinization of the distal nail matrix may also be noted (Fig. 17.6) and moves distally with nail growth.

In most cases, leukonychia involves all fingernails and may coexist with melanonychia (Figs 17.1, 17.5). It has been described in association with numerous chemotherapeutic agents but generally develops when chemotherapy is used in combination. Systematic screening for associated hypoalbuminemia should be performed in this context.

Brittle nails and decreased nail growth

A decrease in nail plate growth is commonly noted with chemotherapy, although it will usually go unnoticed by patients or physicians. The nails are often fragile and thinner [13], which can lead to koilonychia, onychorrhexis, or onychoschizia after several cycles of chemotherapy (Fig. 17.1).
Taxane onycholysis

Onycholysis is defined by the separation of the nail plate from the underlying nail bed. It usually starts from the distal portion of the nail bed, progresses proximally, and can involve the entire nail with the formation of a space. This may result in the formation of painful subungual abscesses and hemorrhages and/or loss of the nail plate [1]. It is noteworthy that docetaxel and paclitaxel are the chemotherapeutic agents that most frequently induce this nail toxic effect, and severe onycholysis almost exclusively occurs with taxanes [14, 15]. Mild to moderate onycholysis, however, may also be noted with other chemotherapeutic agents (e.g. capecitabine, etoposide, cytarabine, cyclophosphamide, doxorubicin, or combination therapy) [1, 2, 16].

Taxane-related onycholysis represents one of the most prevalent adverse events induced by docetaxel or paclitaxel [14]. Recently, the overall incidence of taxane-induced nail changes has been systematically investigated [17]; all-grade incidence was 43.7% and 34.9% with paclitaxel and docetaxel, respectively. Nail lesions are evident after several weeks of treatment [4] because of the slow growth rate of the nail plate. The development of nail changes is strongly associated with weekly administration, the number of chemotherapy cycles given, and cumulative dose of taxanes [2–4, 18]. Although it is more common in patients receiving the once-weekly regimen, it can also be observed with the every 21-day regimen [2, 4].

The onycholytic portion of the nail plate becomes opaque, loses its translucency, and can take on a black, white, or brown-red color (Figs 17.2, 17.3, 17.7). The fingernails are more often involved than toenails and the number of digits affected varies, although involvement may be diffuse. Onycholysis is initially asymptomatic; however pain may occur due to acute trauma, progression of the detachment, or development of subungual hemorrhagic blisters or abscesses with purulent discharge (Fig. 17.8) [1, 14]. The ventral part of the detached plate may also collect debris, and secondary bacterial or fungal infections may develop. Cosmetic and functional impact depend on the number of the nails involved [4], the severity of the detachment, and the extent of pain. Taxane-related onycholysis is sometimes associated with inflammatory erythema of dorsal hands or perimalleolar and Achilles areas (PATEO syndrome: periarticular thenar erythema with onycholysis) (Fig. 17.9) [14, 16]. Finally, the nail matrix (melanonychia, true leukonychia,
Beau’s lines and onychomadesis, brittle nails with ridging and thinning, onychorrhexis, koilonychia) or the periungual tissue (paronychia or pyogenic granuloma) may also be affected at the same time with taxane therapy [3, 14–16].

The pathophysiological origin of taxane-induced onycholysis is not clearly established. It may be the result of direct cytotoxic damage to the nail bed epithelium with epidermolysis and the secondary loss of adhesion of the nail plate to the nail bed [3, 16]. An intrinsic antiangiogenic activity of taxanes has also been postulated [14]. Similarly, a phototoxic mechanism for photo-onycholysis has been advanced by some authors but remains to be confirmed [18]. Lastly, unilateral onycholysis has been reported in patients suffering from contralateral peripheral palsy, suggesting a taxane-induced neurotropic effect (neurogenic or prostaglandin-mediated inflammation) [19] (Fig. 17.9). More recently, Schepisi et al. hypothesized that paclitaxel-related onycholysis may be directly correlated to the duration of the infusion. Indeed, onycholysis may develop more frequently with a shorter infusion (1 hour) than with prolonged infusion, because of increased systemic exposure to the Cremophor vehicle (paclitaxel solvent) [20]. It may explain, at least in part, the higher incidence seen in patients receiving the weekly paclitaxel regimen (1-hour infusion) in comparison with the every 3-week regimen (3-hour infusion).

Nab-paclitaxel is a novel, solvent-free, albumin-bound, colloidal suspension (130nm) of paclitaxel [21]. Since it is devoid of Cremophor EL, several significant adverse events such as hypersensitivity reactions [21] are less likely to develop. Nail toxic effects have only been sporadically reported with nab-paclitaxel [20], especially onycholysis, and are easily manageable. The overall incidence of all-grade nail changes with nab-paclitaxel is significantly lower in comparison with paclitaxel or docetaxel (19.4%) [17].

The impact of taxane-related onycholysis varies but lesions can be tender and painful and may affect patients both cosmetically and functionally in their daily activities, resulting in treatment interruptions. Therefore, management of onycholysis depends on the clinical grading (i.e. National Cancer Institute CTCae) and impact on activities of daily living (Table 17.1). Patients should avoid any damaging or irritant regimen, including manipulation of the cuticles and nail biting, use of fingernails as “tools,” prolonged soaking in water, exposure to solvents or hard chemicals, and application of artificial nails (Box 17.1). In addition, it has been demonstrated that the preventive use of frozen gloves/socks allowed a significant reduction in nail changes from 51% to 11% in fingernails, and from 21% to 0% in toenails [22]. Therefore, the preventive use of frozen gloves/socks should be advised in patients treated with taxanes. Alternatively, the use of ice packs may be a less expensive and effective strategy with similar efficacy. In addition to preventing nail toxicities, frozen gloves or ice packs have been shown to decrease the incidence of peripheral neuropathy, another potentially dose-limiting adverse event. While discontinuation of chemotherapy is only rarely necessary, dose interruptions or reductions may sometimes be required.

Once onycholysis develops, it may be necessary to remove the nail plate (partially or totally) in cases of severe and/or painful lesions, or when associated with a pressure hematoma or subungual abscess. The nail bed must be cleaned and cultured at the same time, and any infection should be promptly treated with topical/oral antibiotics. The nails should be cut regularly until the
nail plate grows and covers the nail bed. Onycholysis is slowly reversible after treatment discontinuation. However, chronic onycholysis can lead to nail bed keratinization and persistent subungual hyperkeratosis [13, 14] (Fig. 17.10a,b). Therefore, it is critical to promote nail reattachment as early as possible by preventing further toxicity and treating underlying infections, otherwise onycholysis may become permanent.

| Grade 0* | Preventive nail care instructions given (see Box 17.1) – frozen gloves should be considered |
| Grade 1* | Continue drug at current dose and monitor for change in severity; obtain bacterial/fungal cultures if infection is suspected; apply topical antibiotics or antifungal agent. Reassess after 2/3 weeks. If reaction worsens proceed to next step |
| Grade 2* | Continue drug at current dose and monitor for change in severity; obtain bacterial/fungal cultures if infection is suspected. If infection, begin oral antibiotics with anti-*Staphylococcus aureus* and gram-positive coverage. If painful hematoma or subungual abscess is suspected, partial or total nail avulsion is required. Pain control. Reassess after 2 weeks: if reactions worsen or do not improve interrupt treatment until severity decreases to grade 0–1 |
| Grade 3* | Interrupt treatment until severity decreases to grade 0–1, obtain bacterial/fungal cultures if infection is suspected, and continue treatment of nail reaction with the following: If infection, begin oral antibiotics with anti-*Staphylococcus aureus* and gram-positive coverage. If painful hematoma or subungual abscess is suspected, partial or total nail avulsion is required. Pain control. Reassess after 2 weeks; if reactions worsen or do not improve, please consider dose interruption or discontinuation per protocole and switch to another antineoplastic agent |

*From nail loss clinical grading, CTCae, V4.02

Table 17.1 Proposed algorithm for taxane-related onycholysis.

**ADL**, activities of daily living.

**Figure 17.10** (a) Persistent onycholysis after chemotherapy; (b) visible subungual hyperkeratosis.
Nail changes induced by targeted therapies (Table 17.2)

Paronychia and pyogenic granuloma

Periungual lesions, which result from damage to the perionychium and manifest as paronychia and/or pyogenic granuloma-like lesions, are frequently observed with targeted anticancer therapies, especially with drugs that target ErbB1 (HER1 or EGFR) receptors, either monoclonal antibodies or tyrosine kinase inhibitors [1, 23–27]. Although periungual lesions occur less frequently than EGFR-induced acne-like rash, they represent one of the cardinal symptoms of cutaneous toxicity described with EGFR (HER1) inhibitors (acute folliculitis, paronychia, hair changes, painful fissures of the fingertips/heels, and skin dryness) [28]. A meta-analysis estimated that all-grade periungual lesions with EGFR inhibitors occur in 17.2% of patients, with a relative risk of 76.94 (95% CI: 40.76–145.22, p < 0.001) [29]. High-grade lesions were estimated to occur in 1.4% of patients. These class-related adverse events are tumor-independent, and are also seen with the use of the most recent ErbB inhibitors targeting several HER receptors (e.g. lapatinib or pertuzumab). In addition, they appear to be more frequent with the newly-approved irreversible ErbB family blockers (dacomitinib, afatinib) [30].

The pathophysiological mechanism underlying the development of paronychia remains speculative. It is thought to result from inhibition of the EGF receptor and downstream EGFR-dependent pathways in basal and suprabasal keratinocytes. This leads to altered differentiation and migration of epidermal cells associated with both inhibition of keratinocyte proliferation and decreased cell survival through the induction of apoptosis [31]. As a consequence, the periungual stratum corneum becomes thinner, which may lead to piercing of the perionychium by the nail plate (onychocryptosis), inducing a secondary inflammatory foreign body-like reaction.

More recently, similar periungual lesions were also described with MEK inhibitors, including selumetinib, cobimetinib, and trametinib [32]. The frequency and severity of these lesions is lower than that occurring with EGFR inhibitors. This nail toxicity probably results from the direct inhibition downstream of the intracellular MAP kinase pathway. In the same way, MEK inhibitors also induce acne-like rash, painful skin cracking, and hair changes similar to those seen with EGFR inhibitors. Finally, mTOR inhibitors (everolimus and temsirolimus) can also induce periungual lesions with similar clinical features [33].

EGFR inhibitor-induced periungual lesions develop gradually after several weeks or months of treatment. This is therefore a relatively late-onset toxicity compared to acne-like rash, which starts within the first days or weeks of treatment [23–25, 28]. Lesions first manifest as acute paronychia, a painful erythematous inflammation with swelling and tenderness of the lateral nail folds. Exudation and easy bleeding may also occur. Paronychia can progress into the formation of friable granulation tissue on the lateral folds of the nail mimicking ingrown nails. These lesions can appear on any digit, but the thumbs and to an even greater extent the great toes are the most frequently affected (Fig. 17.11a–e), probably due to repeated microtrauma. The patient’s quality of life may be negatively impaired, with a deleterious impact on instrumental or self-care activities of daily living [26, 34, 35]. Periungual lesions represent one of the major dermatological burdens identified by patients treated with EGFR inhibitors [36].

Although the lesions are initially sterile, bacterial infections due to Staphylococcus aureus are common (about 25%) and sometimes associated with a purulent discharge. They rarely lead to local or systemic complications. Candida albicans or Pseudomonas aeruginosa infections have also been described [37].

Preventive measures should be systematically advised (Box 17.1), including the avoidance of repeated trauma or friction, washing with soap and water, referral to a podiatrist to correct nail curvature, the use of antimicrobial soaks on a daily basis, and bacterial cultures in case of purulent discharge. Patients should be closely monitored for the early signs suggestive of pyogenic granuloma. The therapeutic strategy should be chosen according to the impact on a patient’s quality of life, the number of digits involved, duration of lesions, and the overall prognosis of the underlying disease. It is also important to keep in mind that pyogenic granuloma-like lesions are dose dependent and partially regress following a dose reduction or temporary interruption of treatment. If the lesions remain self-limited, a conservative management can be proposed in order to reduce periungual inflammation and granulation tissue: high-potency topical corticosteroids alone or in combination with topical antibiotics (e.g. fusidic acid/mupirocin ointment with betamethasone/clobetasol), silver nitrate chemical cauterization, and correction of nail curvature (podiatrist, tapering with stretchable tapes).

However, surgical treatment (under local anesthesia) is sometimes indicated for cases that do not respond to topical measures or that may result in anticancer therapy interruption. It may include limited surgical curettage with partial nail plate avulsion or removal of a longitudinal segment of the nail together with the matrix, with physical destruction of excessive granulation tissue and/or chemical cauterization (with saturated 88% phenol) [1, 26, 38].

Other nail changes

Thin, brittle nails and onycholysis

Anti-EGFR, MEK, and mTOR inhibitors can induce progressive thinning of the nail plate, together with onychoschizia, onychorrhexis, or mild distal onycholysis.
Table 17.2 Main nail toxic effects induced by targeted anticancer therapies.

<table>
<thead>
<tr>
<th>Targeted therapy</th>
<th>Target</th>
<th>Drug</th>
<th>Nail changes</th>
<th>Other dermatologic toxicities</th>
<th>Brand name</th>
</tr>
</thead>
<tbody>
<tr>
<td>Anti-EGFR</td>
<td>EGFR (HER1 or ErbB1)</td>
<td>Cetuximab</td>
<td>Paronychia</td>
<td>Acne-like rashes</td>
<td>Erbitux</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Panitumumab</td>
<td>Pyogenic granuloma</td>
<td>Hair changes (alopecia, eyelash trichomegaly, hypertrichosis, curly hair)</td>
<td>Vectibix</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Erlotinib</td>
<td>Slow growth rate</td>
<td>Xerosis and fissures</td>
<td>Tarceva</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Gefitinib</td>
<td>Mild onycholysis</td>
<td>Mucositis</td>
<td>Iressa</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Necitumumab</td>
<td>Thin nails</td>
<td>Pruritus</td>
<td>Portrazza</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>Brittle nails</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Anti-HER2</td>
<td>HER2</td>
<td>Trastuzumab</td>
<td>Thin nails</td>
<td>Lichenoid reaction, pruritus</td>
<td>Herceptin</td>
</tr>
<tr>
<td>Anti-HER</td>
<td>HER1–4 (ErbB1–4)</td>
<td>Lapatinib</td>
<td>Paronychia</td>
<td>Acne-like rashes</td>
<td>Tyverb</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Afatinib</td>
<td>Pyogenic granuloma</td>
<td>Hair changes (alopecia, eyelash trichomegaly, hypertrichosis)</td>
<td>Giotrif</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Dacomitinib</td>
<td>Slow growth rate</td>
<td>Xerosis and fissures</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>Thin nails</td>
<td>Mucositis</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>Mild onycholysis</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>Brittle nails</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Anti-MEK</td>
<td>MEK 1/2</td>
<td>Trametinib</td>
<td>Paronychia</td>
<td>Acne-like rashes</td>
<td>Cotelllic</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Cobimetinib</td>
<td>Pyogenic granuloma</td>
<td>Hair changes (alopecia, eyelash trichomegaly, hypertrichosis)</td>
<td>Mekinist</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Selumetinib</td>
<td>Slow growth rate</td>
<td>Xerosis and fissures</td>
<td>Under development</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>Thin nails</td>
<td>Mucositis</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>Mild onycholysis</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>Brittle nails</td>
<td></td>
<td></td>
</tr>
<tr>
<td>mTOR inhibitors</td>
<td>mTOR</td>
<td>Everolimus</td>
<td>Paronychia</td>
<td>Acne-like rashes</td>
<td>Afinitor</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Temsirolimus</td>
<td>Pyogenic granuloma</td>
<td>Pruritic maculopapular rashes</td>
<td>Torisel</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>Slow growth rate - thin nails</td>
<td>Apthous -like stomatitis (MIAS)</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>Mild onycholysis</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>Brittle nails</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>Yellow nail discoloration</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Angiogenesis multikinase inhibitors</td>
<td>VEGFR 1–3; PDGFR α/β and other molecular targets (c-KIT, RET, Flt3, CSF-1R, RAE, FLT-3)</td>
<td>Sunitinib</td>
<td>Splinter subungual hemorrhage</td>
<td>Hand-foot skin reaction</td>
<td>Sutent</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Sorafenib</td>
<td>Brittle nails</td>
<td>Skin and/or hair discoloration</td>
<td>Nexavar</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Cabozantinib</td>
<td></td>
<td>Eruptive nevi and keratoacanthoma</td>
<td>Cometriq</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Axitinib</td>
<td></td>
<td>Xerosis</td>
<td>Inlyta</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Pazotinib</td>
<td></td>
<td>Peripheral edema</td>
<td>Votrient</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Regorafenib</td>
<td></td>
<td>Geographic tongue</td>
<td>Stivarga</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>Stomatitis</td>
<td></td>
</tr>
<tr>
<td>RET inhibitor</td>
<td>EGFR, VEGFR 2/3, RET</td>
<td>Vandetanib</td>
<td>Paronychia</td>
<td>Wide range of phototoxic reactions</td>
<td>Caprelsa</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>Pyogenic granuloma</td>
<td>Acne-like rash</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>Photooxycholysis</td>
<td>Hyperpigmentation and blue dots</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>Splinter subungual hemorrhage</td>
<td>Hand-foot skin reaction</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>Xerosis</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>Hair changes</td>
<td></td>
</tr>
<tr>
<td>BCR-ABL inhibitors</td>
<td>BCR-ABL, c-KIT, PDGFR</td>
<td>Imatinib</td>
<td>Melanonychiasis</td>
<td>Pigmentary changes</td>
<td>Gleevec</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>Lichenoid reactions</td>
<td>Cutaneous and mucosal lichenoid reactions</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>Maculopapular rash</td>
<td></td>
</tr>
<tr>
<td>Bruton inhibitors</td>
<td>Bruton tyrosine kinase</td>
<td>Ibrutinib</td>
<td>Brittle nails</td>
<td>Bruising</td>
<td>Imbruvica</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>Onychoschizia</td>
<td>Target-like hematoma</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>Onychorrhexis</td>
<td>Maculopapular rash</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>Mild onycholysis</td>
<td>Straightening and softening of the scalp hair</td>
<td></td>
</tr>
<tr>
<td>Pan (selective) FGFR inhibitors</td>
<td>FGFR 1–4</td>
<td></td>
<td>High-grade onycholysis</td>
<td>Hair changes (eyelash trichomegaly, alopecia, straightening of the scalp hair)</td>
<td>Under development</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>Onychomadesis</td>
<td>Xerosis</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>Beau's lines</td>
<td>Xerostomia</td>
<td></td>
</tr>
</tbody>
</table>

EGFR, epidermal growth factor receptor; FGFR, fibroblast growth factor receptor; HER, human epidermal growth factor receptor; MEK, mitogen-activated protein kinase; mTOR, mammalian target of rapamycin; PDGFR, platelet-derived growth factor receptor; RET, rearranged during transfection; VEGFR, vascular endothelial growth factor receptor.
These lesions are less severe in comparison with cytotoxic chemotherapeutic agents. Patients also face a slower nail growth rate. Symptomatic interventions may be needed (Box 17.1).

**Splinter subungual hemorrhages**

These are almost exclusively observed with angiogenesis inhibitors inducing a dual inhibition of vascular endothelial growth factor (VEGF) and platelet-derived growth factor (PDGF) receptors (i.e. sunitinib, sorafenib, pazopanib, axitinib, regorafenib, cabozantinib). The incidence of these hemorrhages ranges from 12% to 70% [40, 41]. They present as painless, red or brown/black longitudinal lines which develop after several weeks and chiefly involve fingernails. They are similar to splinter hemorrhages described in association with bacterial endocarditis or antiphospholipid syndrome but are not associated with distant thromboembolic events. They disappear spontaneously (growing out with nail growth) and do not require specific management or treatment discontinuation [42].

**Melanonychia**

This occurs far less frequently than with cytotoxic chemotherapeutic agents and has been mainly described with the BCR-ABL inhibitor imatinib. Longitudinal, transverse, or total melanonychia has been reported with imatinib. It may be related to the temporary blockade of c-KIT receptor. Melanonychia may be associated with mucosal or skin pigmentary changes in this context [43].

**Yellow nails**

Diffuse yellow nail discoloration has been sporadically reported with mTOR inhibitors (everolimus) [44].

**New targeted anticancer therapies**

**Ibrutinib**

Ibrutinib is a first-in-class, oral covalent inhibitor of Bruton’s tyrosine kinase (BTK), a critical mediator of the B-cell-receptor signaling pathway implicated in the pathogenesis of B-cell cancers. It is now approved by the US Food and Drug Administration (FDA) and European...
Medicines Agency (EMA) for the treatment of chronic lymphocytic leukemia, Waldenström’s macroglobulinemia, or refractory and relapsed mantle-cell lymphoma.

Bruising with characteristic target-like hematomas and maculopapular rashes represent the most representative skin toxic effects induced by this new targeted agent [45, 46]. A progressive development of brittle fingernails is also reported in about two-thirds of treated patients [47]. Lesions usually remain self-limited but onychoschizia, onychorrhexis, and even mild onycholysis can be observed. These nail changes become apparent after several months of treatment (median 6–9 months). In addition, hair changes may be associated in 25% of cases, mainly in the form of grade 1 alopecia and softening and straightening of scalp hair [47].

Ibrutinib acts in inhibiting BTK by covalently binding to cysteine 481. It may also bind and alter cysteine residues of hair and nails. Biotin supplementation may be prescribed in this context.

Vandetanib
The new oral multikinase inhibitor vandetanib specifically targets the RET (rearranged during transfection) protooncogene, EGF and VEGF receptors. It is now approved for unresectable, locally advanced, or metastatic medullary thyroid carcinoma. Skin toxic effects are among the most prevalent adverse events associated with vandetanib therapy, which are mostly correlated to direct inhibition of VEGF or EGF signaling pathways. For instance, subungual splinter hemorrhages (VEGFR inhibition) and paronychia/pyogenic granuloma (EGFR inhibition) affect 5% and 11% of patients, respectively [48]. Vandetanib, which is a low-molecular-weight molecule with a polycyclic structure containing unsaturated double bonds, can also induce photosensitivity reactions [48, 49]. Indeed, more than one-third of patients present UVA-induced phototoxic reactions, including exaggerated sunburn response, blue-gray hyperpigmentation with visible blue dots, lichenoid photodermatitis, or photo-induced erythema multiforme. In the same way, we have recently reported several patients developing a moderately painful type 1 photoonycholysis, combining a characteristic medial onycholysis with sparing of the lateral parts of the fingernail plates [50] (Fig. 17.12). This vandetanib-related nail toxicity is probably underdiagnosed. Preventive measures should include strict patient education about UVA/UVB photoprotection from the initiation of vandetanib therapy and early detection. Of note, photoonycholysis had never been reported so far with other anticancer-targeted therapies.

Selective pan-FGFR inhibitors
Fibroblast growth factor (FGF) and its transmembrane receptor tyrosine kinases (FGFR) play a critical role in several cancer types and selective pan-FGFR inhibitors represent promising agents in cancer management [51]. Recently, potent selective pan-FGFR (1–4) tyrosine kinase inhibitors have been developed and are currently under clinical investigation in a number of solid tumors harboring FGFR pathway alterations (e.g. glioblastoma, urothelial bladder, breast, gastrointestinal, or endometrial cancers). Preliminary results suggest a challenging but manageable safety profile. These drugs, however, are associated with a wide range of dermatological mechanism-based toxicities. These mainly include alopecia and hair changes (straightening of scalp hair, eyelash trichomegaly), stomatitis with xerostomia, and nail toxic effects. For instance, dose-dependent nail changes including onycholysis, onychodystrophy, onychalgia, and nail bed infections were among the most common treatment-related adverse events reported in the phase I dose-escalation study with the first-in-class pan-FGFR inhibitor JNJ 42756493 (35% and 6% of all-grade and high-grade incidence, respectively) [52]. We have also observed severe onycholysis affecting toenails and fingernails in patients treated with two other selective pan-FGFR inhibitors (AZD4547, BGJ398) [53]. These nail lesions were very similar to taxane-related onycholysis. By contrast, nail toxicities have not previously been described with non-selective FGFR tyrosine kinase inhibitors such as dovitinib and lucitanib. These data strongly suggest a mechanism-based class-specific adverse event related to the selective inhibition of the FGFR signaling pathway.

Figure 17.12 Vandetanib-related photoonycholysis (type 1). Note the sparing of the lateral parts of the nail plate and the Pseudomonas aeruginosa colonization.
Cancer immunotherapy

Caroline Robert

Few nail changes or toxicities have been reported with cancer immunotherapy, in contrast to the plethora of nail adverse events that are observed with classical chemotherapy or with kinase targeting agents.

Cancer immunotherapy with checkpoint inhibitors – anti-CTLA-4, ipilimumab (Yervoy, BMS), anti-PD1, pembrolizumab (Keytruda, MSD), and nivolumab (Opdivo, BMS) – is revolutionizing the field of cancer therapy. Indeed, since their efficacy was demonstrated (Opdivo, BMS) – is revolutionizing the field of cancer therapy, these drugs, used as monotherapy or in combination, are now being evaluated in many other tumor types with highly promising results [54–58].

References


Checkpoint inhibitors induce a wide spectrum of adverse events that are related to their mechanism of action, i.e. the stimulation of the immune system [59]. Most of them present as autoimmune manifestations: vitiligo, inflammatory bowel disease, endocrinopathies, or arthralgias. Non-specific rashes are among the most frequent immune-related adverse events observed with these monoclonal antibodies. Psoriatic and lichenoid reactions have also been reported, however, their incidence is unknown [60–64]. Few clinical reports concern patients presenting with specific nail changes in the context of immunotherapy.

Nail hyperpigmentation has been reported with interferon [65]. With the checkpoint inhibitors, anti-CTLA-4 and anti-PD1, nail involvement can be seen in association with immune-related cutaneous manifestations such as lichenoid or psoriatic rashes or alopecia areata.


Definition

Occupational nail disorders represent those abnormalities of the nail apparatus produced or aggravated by the working environment. The predisposing factors are those for occupational disorders elsewhere, that is:

- inexperienced workers
- inadequate personal hygiene
- excess use of irritants
- temperature and humidity
- inadequate protection.

Accurate diagnosis depends on:

- appearance
- disappearance and relapse of the nail condition
- location of the lesion
- patient’s history.

Diagnosis of occupational nail disorders

The fingernails are used as “tools” in many occupations [1–4] and the way they look is of importance in all occupations where personal contact occurs. Nail disorders can therefore be more disabling at work than might at first appear. Most nail disorders are confined to the hands.

The subject of the first part of this chapter is the wide range of nail disorders that are primarily caused by the working environment. Some of these look very like certain endogenous (constitutional) nail disorders. This makes their diagnosis more difficult. Nail changes in dermatoses such as psoriasis, tinea, and lichen planus may be misinterpreted as being caused by work. Conditions such as psoriasis of the nails may, however,
be exacerbated by occupational trauma or this may even precipitate an underlying tendency to the disease (isomorphic phenomenon); in patients with rheumatoid arthritis, lichen planus, and secondary syphilis, Koebner phenomenon may occur [5]. Atopic dermatitis should always be sought and the most important aspect in a history for preemployment screening is that of severe childhood eczema [6].

**Etiology**

Frequently the causes of occupational nail disorders are multifactorial. They can occur at any age, but there is widely thought to be a bimodal distribution of peaks in incidence of dermatitis, the first occurring in the early years of the job and the second in middle age. In women their frequency is twice as high as in men [6].

In assessing a nail condition suspected of being occupational:

- Visualize what the hands do at work.
- Look for functional distribution (commonly, the first three fingers of the dominant hand).
- Check for occupational stigmas of the nails.
- Examine the whole of the skin surface. This should never be omitted as the correct diagnosis may be evident at a site very distant from the nails.
- Ask about the presence of similar nail conditions in coworkers and about hobbies with potential chemical or metal exposure [7].

Thorough investigations are necessary to identify the allergens and/or irritants that may be causing the nail disorders. Although still a research tool, estimation of the levels of metals such as arsenic and nickel in the fingernails may be a useful indicator of occupational exposure [8, 9].

There are also some laboratory tests, such as mycological and bacteriological examinations, which are essential diagnostic aids. A punch biopsy of the nail can sometimes additionally assist. A radiograph of the terminal phalanx is occasionally relevant, for example exostosis of occupational origin.

The final diagnosis may require a workplace visit.

**Handicap, impairment, and disability**

Handicap describes the effect on the patient’s normal functioning in society as a result of the disability, while impairment is the effect of the disease process on the diseased organ (e.g. persisting fissures on the fingertips). Disability describes the functional effect of this impairment and so, in the above example, the disability might be that the patient could not use a keyboard because of the pain and disordered sensation of the fingers resulting from the disease [10].

**Clinical reaction patterns**

Reaction patterns that can be seen clinically include:

- changes in the texture and contour of the nail plate, onychauxis, worn-down nail plate (usage des ongles), brittle nails, koilonychia, clubbing, and pseudoclubbing
- changes in the surface of the nail plate and its attachments, resulting from direct trauma, matrix involvement, or paronychia with sometimes onychomadesis leading to nail shedding
- changes in the surrounding tissue (pulpitis)
- changes in color with nail plate staining or subungual alteration
- distal bony phalanx anomalies.

**Occupational nail hazards**

**Traumatic abnormalities**

This is one of the most important groups of occupational disorders and includes major trauma, repeated microtrauma, and foreign body injury.

**Acute major trauma**

The level of the nail bed injury is the critical factor in deciding the requirement for nail bed management. Nail stability requires at least 5 mm of healthy nail bed, distal to the lunula, for nail adherence [11]. Acute injury may be associated with partial or total hematoma (25% of the surface of the visible nail plate), lacerating wounds, fractures of the terminal phalanx, denudation of the distal phalanx (nail degloving) and foreign bodies.

**Delayed postacute traumatic deformities**

These may be associated with onycholysis, dorsal pterygium, split nail deformity, various nail dystrophies, and hooked nail.

**Repeated microtrauma**

Repeated microtrauma may be associated with koilonychia, fingernail fragility, toenail dystrophy, and onycholysis of mechanical origin, and may be caused by foreign bodies.

*Friction and pressure* gradually wear down the nail and are characteristic of particular occupations such as pottery workers (Fig. 18.1) and workers who repeatedly lift heavy bags [12]. Onycholysis, koilonychia, longitudinal
splitting, and occasional splinter hemorrhages may also be seen. Subungal hemorrhages have been reported from the USA in three inexperienced male dishwashers using heavy rubber gloves while working [13], and are frequent in sportsmen’s toes [14, 15] and in the toes of dancers, where there may be associated subungal exostosis [16]. Slaughterhouse workers, manually skinning cattle, develop a rectangular onycholysis of the central nail plate and, in one case, necrosis of the nail bed was reported [17] (Fig. 18.2a,b). A peculiar artifact of Japanese brocade weavers presents with two comb-like filed nails [2].

Multiple myxoid cysts may be secondary to occupation [18]. They developed within 12 months of a patient starting a job that involved pushing a garment into an embroidery mold, thus extending a downward force on the fingertips.

Transverse leukonychia has been described in Japan from the mechanical pressure of keypunching [19]. But is slot machine finger an occupational dermatosis [20]?

Repeated low-grade frictional trauma occurs in a multitude of occupations [21]. In a carpenter, for example, scaling, erythema, and fissuring involved the left thumb and both index fingers on areas corresponding to those used to grip the nails and screws.

In tailors, who use the dorsum of the nails to smooth the cloth while sewing, worn-down nails show a triangular area of marked thinning with its base lying at the free edge of the nail plate and sometimes a wedge-shaped incisure [22].

Mechanical trauma associated with thermal injury has produced fissured, scaly patches on the pulps of toast-makers’ fingers [23].

Due to mechanical forces, significant effects on fingernail curvature were observed in carpenters and jazz bassists [24].

Removing the plastic corners from patch-test strips has been described as the cause of symmetrical indentations of the radial free edges of both thumb nails [25].

Vibrating power tools, such as pneumatic drills and chainsaws, cause nail thickening, brittleness, and splitting of the free edges. Yellow-white longitudinal bands may extend distally from the lunula, sometimes becoming confluent. Distally the nails become darkly tinged and may turn black. The nail plate may develop ridging and eventually be shed entirely [26]. The same stimulus causes Raynaud phenomenon in the skin (vibration white finger), especially when vibrating power tools are operated in cold climates [27, 28], or in carpal tunnel syndrome [29, 30]. The hand that holds and guides the tool is often more severely affected.

Until more is known of the pathophysiological mechanisms behind the disease, the patient’s description of their symptoms, combined with a detailed exposure history, will remain essential for a diagnosis of vibration injury irrespective of the results of the tests used [31].
Raynaud phenomenon has also been seen in typists, violinists, and pianists.

Sports-related trauma

Sports-related trauma occurs frequently. In golfer’s nails, distal splinter hemorrhages are seen, especially in the fingers used most strongly in the golf grip hand [32]. Catching a frisbee may produce repeated minor damage to the nail plate – frisbee nail [33].

Judo can be responsible for trachyonychia. The frequent grabbing of the opponent’s jacket accounts for the rough “judo” nails [34]. Karate may produce clubbing; in addition, professional and recreational karate enthusiasts are likely to injure the nail matrix as a consequence of the sharp, strong blows to which their fingernails and toenails are prone. Clinically, this presents as leukonychia, usually in transverse bands [35].

Tennis and squash players, in whom sudden, abrupt changes in foot direction occur, develop tennis toe and may exhibit subungual hemorrhages. Soccer players and joggers can suffer the same complications.

Musician-related trauma

Playing the piano can produce a vasospastic white finger disease as well as paronychia. The harp can also be responsible for paronychia associated with onycholysis and subungual hemorrhages [36]. The violin may induce paronychia. Friction as a cause of irritant contact dermatitis may be observed in guitar players whose fingers are used to pluck the strings. Acroosteolysis associated with pain in the distal fingers has been reported [37]. To play the viola, one must make a repetitive compression and pluck the strings, with the distal portion of the fingers, especially the nails, presenting brittleness and a worn-down appearance [38]. Worn-out thumbnail may be a stigma in guitar players (Fig. 18.3a,b). The right thumbnail may show onychodystrophy mediana canaliformis in professional guitarists or changes similar to the habit–tic deformities [39].

Foreign body injury

Exposure to certain plants and woods may cause foreign body injury (see “Sensitizers”). Thorns, thistles, and sharp-edged leaves may injure the nails, especially cactus thorns in desert areas. Secondary infection is a likely complication.

Hyacinth and narcissus bulbs possess raphide cells containing bundles of needle-shaped crystals of calcium oxalate. These crystals readily penetrate the periungual skin, causing erythema and edema with pain and itching [40]. Dieffenbachia seguine belongs to the Araceae family and is used as a floral room decoration. During a 10-year period, 61 200 cases of poisoning were recorded in the USA. The main symptoms are oral irritation, vomiting, and diarrhea. Dieffenbachia cells contain needle-like calcium oxalate crystals that are released upon injury and penetrate the skin and mucosa. In fingertip necrosis after contact with Dieffenbachia, guttation fluid penetrates into the dermal compartments through a rhagade [41]. Paronychia associated with daffodil pickers’ rash has been reported [42].

Glass fiber, above approximately 5 µm in diameter, mechanically irritates the periungual tissue. Paronychia may result from the penetration of glass spicules beneath the surface of the nail bed.

Figure 18.3 (a,b) Occupational stigmas in a guitar player using a thumbpick. Courtesy of C. Romaguera.
the proximal nail fold. It may also cause onycholysis with darkening of the nail plate [43]. Implantation of hair beneath the nail may produce onycholysis [44] and even subungual trichogranuloma. Chronic paronychia sometimes appears in hairdressers [45].

An unusual case of chronic paronychia in a female hairdresser occurred as a consequence of a hair shaft penetrating beneath the nail fold [46]. This may require surgical management in recalcitrant cases [47].

Vicuñaller’s thumbnail, a condition of subungual osmotrauma, is the consequence of small foreign bodies of dehydrated food becoming embedded below the nails [48].

Physical hazards

Burns, when mild, cause onycholysis. When severe, disfiguring scars, pterygium, and fissured nails may result.

Prolonged exposure to cold may result in injury to the nail matrix, leading to derangement of the nail plate ranging from Beau’s lines to complete shedding. Cold injury, particularly to peripheral parts, is common among such groups as soldiers on active service although adequate protective measures now make this rarer than in the past. Conditions such as trench foot, acute pernio (chilblains), and frostbite [49] may damage the nail apparatus. Seasonal koilonychia in Ladakh, in north-west India [50], is due to exposure to cold water while hand washing clothes and to wet mud while repairing walls and irrigation canals.

Frostbite, the freezing of tissues in response to cold air, metals, or liquids, may cause tissue loss due to vasospasm with thrombus formation and extracellular ice crystal formation. Venous pressure increases, capillary perfusion decreases, and intravascular “sludging” is evident. Depending on the acuteness of the cold injury to the nail apparatus, changes akin to chilblains, Raynaud phenomenon or disease, and early acrosclerosis may be seen, including necrosis or gangrene of skin or deeper tissues. Numbness of the tip of the right index finger and thumb has been noted as a side-effect of cryotherapy in the treating physician. It would seem that even brief contact with the nitrogen-cooled nozzle of a cryosurgical unit is sufficient to induce superficial neural damage in the fingertips, provided that exposure occurs repeatedly [51]. It should be noted that the nail apparatus possesses a good anastomotic blood supply and large numbers of glomus bodies, which help to protect against all but the worst of cold injuries.

Workers dealing with frozen shrimps experience nail dystrophy and paronychia [52].

Ionizing radiation may cause the loss of nails [53], and the late changes of chronic radiodermatitis may give rise to Bowen disease or skin cancer [54] up to 30 years after exposure. The earliest signs are brittleness and longitudinal ridging (Figs 18.4, 18.5). Later the nail plates become dull and slightly opaque with a brownish hue. The skin at a corresponding stage shows atrophy, telangiectasia, and keratoses. The thumb is never involved in radiation dermatitis. A verrucous lesion appearing on the hyponychium or adjacent nail bed may herald the development of malignant change (Fig. 18.6). Minute black spots, known as “coal spots,” appear beneath the nail plate and slowly spread over large areas of nail, often in longitudinal bands. A chronic relapsing paronychia commonly occurs. After a brief episode of acute radiodermatitis, which may elude diagnosis, an asymptomatic period of many months may precede the typical picture of chronic radiodermatitis [55].

Microwave radiation can cause transverse ridging, onycholysis, and other plate dystrophies. Brodkin and Bleiberg [56] reported nail damage in restaurant workers exposed to a faulty microwave oven. They emphasized that the nail matrix may be damaged by microwave-induced thermal injury without the sensation of heat being felt by the oven user.
Sensitizers

While it is debatable whether contact sensitization ever occurs through the nail plate, rather than via periungual skin, the nail plate can certainly be altered by subsequent allergic contact dermatitis. A true, positive patch test typically shows that erythema, papules, or vesicles may spread beyond the test site [57]. Sensitizers causing occupational allergic contact dermatitis in the nail area are discussed next.

Plants and flowers

*Alstroemeria* dermatitis can result in onycholysis, in addition to dermatitis of the thumbs and index fingers [58].

*Hydrangea* dermatitis may present with a clinical picture which includes chronic paronychia and associated nail dystrophy [59]. *Nasturtium*, a common plant used in salads, may produce fingertip dermatitis [60]. *Rhus dermatitis* (from poison ivy, oak, and sumac) may result in onycholysis and a yellowish discoloration of the nail plate [61].

*Tabernaemontana coronaria* has produced a unique fingertip dermatitis of the thumb, index, and middle finger of both hands with itching, erythema, scaling, severe fissuring, and exudation [62].

“Tulip fingers” (Fig. 18.7) is a painful, dry, fissured, hyperkeratotic eczema caused by contact with tulip bulbs. It starts beneath the free margin of the nails and extends to the fingertips and periungual regions. Suppurative granulating erosions may be seen on the fingertips in long-standing cases. At times the face, hands, forearms, and genitals may also become involved. The highest concentration of the allergen, α-methylene-γ-butyrolactone, is to be found in the outermost cell layers of the inner bulb scales [63–65].

Other sensitizers

The wooden orange stick traditionally used for applying cuticle remover has been responsible for a persistent eczema of the right hand in a manicurist [66].

*Turpentine*, the oleoresin from pine trees, is now a much less common sensitizer than it used to be, owing to its gradual replacement as a solvent by less expensive substitutes. In craft workers, it can still occasionally cause an eczema of the periungual tissues and fingers with subungual hyperkeratosis.

Chemicals

*Acrylics*, the methacrylate and acrylate compounds developed during the 1930s, found extensive application in plastic glass for aircraft, paints, coatings, and printing inks, as well as in dentistry. Today, acrylates have a broad area of application in various products, such as the manufacture of dental prostheses and tooth fillings; printing colors; lacquers; paints; orthopedic prostheses and splints; soft contact lenses; histological preparations; floor waxes; floor coatings; surface treatments of leather, textiles, and paper products; nail cosmetics; and as glues, sealants, and adhesives [67]. Repeated contact with acrylic materials, especially the sensitizing liquid monomers, has long been known to be responsible for contact dermatitis in dental staff [68] and orthopedic surgeons [69].

More recently, a wider public has been affected by the practice of wearing sculptured artificial nails [70, 71]. Sculptured nails are marketed as a kit containing an artificial nail called the template, a liquid monomer, and a
Occupational Abnormalities and Contact Dermatitis

powdered polymer (see Chapter 19). By mixing the monomer and polymer together, polymerization is affected because of the presence of an organic peroxide catalyst and an accelerator. The material can be molded onto the client’s natural nail and hardening occurs at room temperature or in a photobonding box [72]. First, the natural nail is roughened with a burr. Then it is painted with the acrylic compound to produce, on hardening, an artificial nail. This is gradually enlarged and elongated by repeated applications. The prosthesis can be filed and manicured to the desired shape and as the nail plate grows out, further infillings of acrylic can be made to maintain the natural contour.

Beside the self-curing acrylate-containing artificial nails, UV-cured sculptured nails (nail gels) [73, 74], and French manicure (consisting of a natural, pink, beige, or nude base with pure white at the distal end), which at first mainly affected nail beauticians [75], the more recent introduction of light-cured nail polishes that are more durable and long-lasting than the conventional nail polishes has considerably increased the incidence of contact allergy to acrylates and methacrylates in consumers as well [76]. This is mainly due to the appearance on the market of different home kits, widely available via the internet, for which a UV light-emitting diode (LED) lamp is used, often providing incomplete cure of the acrylics present in the transparent base and top coat layers [77]. Due to the high frequency of the adverse effects, including onycholysis [76], lesions under the nail plate, and paronychia, with in some cases permanent nail damage with thin, brittle nails, a specific brand was even prohibited in Sweden and, as a result, the EU Commission is gathering information from all member states, with the aim of performing a safety evaluation. The nail damage due to allergic contact dermatitis from acrylic nails may sometimes be misdiagnosed as psoriasis, hence the usefulness of patch testing in such patients.

After a few months of application, patients may begin to show an allergic contact dermatitis, usually of the dorsal aspects of some of the fingers and paronychial tissue, the face, and the eyelids, but sometimes more extensively.

Pain and persistent paresthesia have been reported in a dental nurse [78] but permanent paresthesia may occur without an allergic reaction [79]. Paronychial inflammation may be quite severe: dentist’s occupational allergic paronychia associated with severe fingertip dermatitis can be caused by acrylates (Fig. 18.8). In some cases, sensitization may produce significant economic and mental stress in affected patients. Interestingly, no difference in the occurrence of skin problems was observed between individuals using gloves and individuals who did not use gloves while handling acrylates [80]. Nail discoloration may occur and the nail bed itself usually becomes dry and thickened. Onycholysis of the natural nail occurs with thinning and splitting. This disfiguration of the nail plate can last for many months.

On patch testing, the patients react strongly to the liquid acrylic monomer but not to the polymer. However, (meth)acrylate-containing products regularly contain undeclared (meth)acrylate compounds. Methylmethacrylate was used historically but in 1976 the Food and Drug Administration in the USA banned its use. Since then, other methacrylates as well as acrylates, dimethacrylates, and trimethacrylates have been used instead, which also sensitize.

Manicurists who apply artificial nails to clients may become sensitized. The thumb and index or middle fingers of the left hand are constantly exposed as the manicurist holds the client’s finger during the process of building up the sculptured nails. Even exposure to the vapor from open bottles may subsequently elicit dermatitis in highly sensitized persons. Loss of fingernails due to persisting allergic contact dermatis in an artificial gel nail designer is rarely reported and the preparation used in the case reported by Haglmüller et al. [81] was a one-component gel based on aliphatic urethaneacrylate, tetraethyleneglycol-diacrylate, and hydroxyfunctional methacrylates.

A laboratory technician working in the manufacture of disposable contact lenses developed neurological and gastrointestinal symptoms after working with UV-curable acrylic monomers. The only skin symptom was transient onycholysis of the fingernails [82].

Industrial sealants that polymerize rapidly under anaerobic conditions in the presence of the metals in steel and brass contain sensitizing dimethacrylates. These products have immensely useful applications in the locking of screws firmly into position. Allergic contact dermatitis from such sealants affects principally the pulps of the fingers and can extend as scaly eczema under the free margin of the nails. Kanerva et al. [83] have reported optician’s occupational allergic contact
dermatitis, paresthesia, and paronychia caused by anaerobic acrylic sealants. Onycholysis has been described in several such patients. Using acrylic resin to repair wind-screens may produce dermatitis of the fingertips, with positive tests for 2-hydroxy-ethylmethacrylate (HEMA) and methylmethacrylate (MMA). Patients working with dental prostheses should be patch tested with MMA, HEMA, dimethacrylates, epoxy acrylates, and urethane acrylates.

Dentin bonding systems seem to be stronger sensitizers than MMA. Furthermore, seven of the 11 patients reported by Kanerva et al. [84] developed paresthesia. Triple-cured hybrid-glass ionomers contain the same sensitizing acrylics, for example dimethacrylates, as dental composite resins and bonding agents. As they are mixed manually, and acrylics rapidly penetrate protective gloves [80], the risk of becoming occupationally sensitized is evident [85]. Thus, no-touch techniques should be used when handling uncured acrylics.

Printing workers sensitized to photopolymerizable acrylic resin may show eczematous lesions on the fingertips and around the nail plate, extending to the distal subungual area [86]. The thumb, index, and middle fingers of both hands are affected with fissuring and scaling [87].

“Caine” local anesthetics, especially amethocaine and procaine, cause an allergic contact dermatitis in dental personnel, particularly on the pulps of the first three digits, due to contact with either the preparatory topical preparation or the liquid to be injected. Propanidid can produce a similar pattern in anesthetists with paronychia, sometimes of both hands [88] (Fig. 18.9).

Cement dermatitis may be allergic, due to the dichromate content, or may result from alkaline irritation and burns. Dermatitis of the dorsum of the proximal nail fold and koilonychia are frequent (Fig. 18.10). The latter is usually accompanied by distolateral subungual hyperkeratosis lifting the lateral edges of the nail. Painful fissures in the same area are common [89].

Codeine sensitization in pharmaceutical workers has been associated with subungual hyperkeratosis, onycholysis, and nail atrophy, as well as dermatitis of the hands, arms, and face [90] (Fig. 18.11).

Epoxy resin dermatitis [91, 92] especially involves the right first two fingertips, producing erosion and crusting or necrotic-appearing lesions [93]. The resin oligomer may collect under the free edge of the nail and polymerize slowly as it dries (Fig. 18.12).

Adhesive containing ethyl-cyanoacrylate used in nail wrapping, in which linen or silk is glued to the abraded nail and filed down, as well as for attaching preformed plastic nails, can cause a periungual contact dermatitis in manicurists and/or clients [94] and in hairstylists attaching pieces of false hair to bald scalps [95]. It spreads to the eyelids and may appear as patches over
the backs of the hands [96], simulating small plaque parapsoriasis [97]. Plate makers and those with food allergy, such as tomatoes, onions (Fig. 18.13), garlic [98–103] (whose major allergen, diallyl disulfide, often affects the first three fingers of the non-dominant hand), may develop finger pulp dermatitis with hyperkeratosis and fissuring, onycholysis, nail transverse depressions, and paronychia [103]. The nails may also present with several transverse depressions. Food handlers who have contact with uncooked food may develop immediate-type hypersensitivity in the form of protein contact dermatitis, a variant of contact urticaria [6]. It is also important that housewives and chefs with hand dermatitis and subungal hyperkeratosis thoroughly avoid contact with Alliaceae vegetables, such as garlic, onion, chives, shallot, and leek, with bare hands.

Formaldehyde (Fig. 18.14) is responsible for sensitization in many occupational groups, including hospital staff, when an eczema of the fingers with nail dystrophy may result [104]. Nail hardeners containing formaldehyde, because of its ability to cross-link with keratin, may also induce nail damage mimicking psoriasis [105].

Glutaraldehyde, the active ingredient in many commonly used cold sterilizing agents, may be responsible for a papulovesicular, scaly, pruritic dermatitis. This was primarily around the fingertips in the case reported by Fowler [106]; onychodystrophy was also noted. Hydroxylamine, which is both a sensitizer and an irritant, may produce onycholysis and/or paronychia [107–109]. It has been widely used in color photograph processing, the chemical industry (oximes synthesis), the pharmaceutical industry (bactericide, fungicide, antialgal), and in the manufacture of rubber and plastic compounds, cosmetics, and soap.

1-Methylquinoloxinium-p-toluene sulfonate sensitization, from a conditioner applied to offset lithography plates in order to render the image receptive to ink, causes dermatitis of the fingertips and periungual areas, particularly of the index, middle, and ring fingers of the right hand [110]. Contact sensitivity to a cycloplegic mydriatic agent and to its pharmacological components tropicamide and phenylephrine hydrochloride was reported on the finger of a nurse. Her work included the instillation of eye drops into patients undergoing routine funduscopic examination. The lesions showed well-demarcated brownish erythema with scaling on the second and third fingers of her left hand. She used these fingers when separating the lids of patients for the instillation of mydriatic drops, some of which leaked on to her hands [111].

Allergic contact dermatitis from nonoxynol-6, a non-ionic emulsifier in an industrial waterless hand cleanser, was associated with a transverse dystrophy of the fingernails [112].

Propacetamol is an analgesic and antipyretic medication that may induce fissured fingertip eczema in nurses preparing injections of this drug [113]. Propolis may produce contact dermatitis in dental technicians [114].

Nail dystrophy and fingertip dermatitis have been seen as a manifestation of methylmethacrylate allergic contact dermatitis in a cow hoof trimmer [115].

Quaternium-15, a broad-spectrum bactericidal formaldehyde releaser, was responsible for throbbing pain and tenderness in fingernails which had gradually become thickened and discolored. Uncommonly seen, it has occurred in hairdressers [116]. During the summer of 1979, women in Britain using adhesive to attach a brand of plastic artificial nails began
to present with onycholysis, subungual hyperkeratosis, atrophy of the nail plate, and dermatitis of the periungual skin [117]. This was traced to contact sensitization by p-tertiary butylphenol (PTBP) formaldehyde resin in a particular batch of the adhesive (Fig. 18.15). This was a particular problem because the patients using these nails tended to have occupations that brought them into the public eye.

Thiourea contained in silver polish may produce contact and photocontact allergy with vesicular eruption of the fingertips and invasion under the fingernails [118].

Unsaturated polyester (UP) resin cements can sensitize car repairers and mold makers, the resulting dermatitis sometimes having an element of subungual hyperkeratosis [119].

**Biological sensitivity**

In *escavenitis* [120] (Fig. 18.16), the coelomic fluid of a sea-worm (*Nereis diversicolor*) used as bait can cause an exudative onychopathy with onycholysis of the first three fingers of the right hand in fishermen.

*Bryozoans* (“moss animals”), invertebrate animals resembling seaweeds, cause contact and photocontact dermatitis with nail involvement, including pitting, paronychia, extensive distal nail dystrophy, and subungual hyperkeratosis [121] (Fig. 18.17).

**Chemical irritants**

An irritant patch test reaction is a sharply demarcated erythema with minimal infiltration and with pustules. The nails can be softened and gradually destroyed by prolonged immersion in water containing high
concentrations of *alkalis, alkaline chlorine-containing compounds* [122], or powerful *detergents* (Fig. 18.18). Irritant reactions appear around and under the nails when the hands come into contact with concentrated enzyme powder. Bleeding ulcerations under the nails may be seen [123].

*Aminoethyl ethanolamine*-containing soldering flux in the electronics industry is usually irritant and may sometimes cause allergic contact dermatitis [124], beginning periungually with onycholysis and spreading down the fingers and patchily onto the backs of the hands.

Permanent wave chemicals (*ammonium thioglycolate*) may cause koilonychia in hairdressers in conjunction with soreness of the distal nail beds, without associated dermatitis [125] (Fig. 18.19). Thioglycolates in depilatories (chemical hair removers) are a further domestic cause of acute chemical onycholysis, several fingernails being involved at the same time.

The application of a solution containing *arsenic, copper acetate*, and *hydrochloric acid*, used to give a patina to belt buckles, produced a marked throbbing pain in the distal phalanx of all the fingers of the right hand after 3 days. A green-blue coloration appeared in the nails, in the surrounding tissues, and in the pulp, together with

Figure 18.16 Fisherman’s dystrophy due to escavenitis. Caused by sea-worm coelomic fluid. Courtesy of P. Angelini.

Figure 18.17 Severe dermatitis and nail dystrophy due to bryozoans. Courtesy of C. Audebert.

Figure 18.18 (a,b) Subungual and fingertip inflammatory eruption due to powerful detergents.

Figure 18.19 Koilonychia in a hairdresser (thioglycolate). Courtesy of L. Kanerva.
edema of the affected region (Fig. 18.20). Onycholysis, slight subungual hyperkeratosis, and acropulpitis were still evident after 6 months [126].

The weedkillers diquat and paraquat can also soften and discolor the nail plate, leading to nail loss [127]. This can happen either from contact with the chemicals in concentrated form [128] or following gross contamination with diluted solutions [129]. Transverse leukonychic band has been observed with paraquat [130]. Discolored changes have also been described in a man using 5% dinitro-orthocresol (Fig. 18.21), without further recommended dilution, for spraying fruit trees [131]. Dinobuton handlers may present with yellow nails and hair [132] (Fig. 18.22).

Enzyme detergents were found to cause acute onychia and onycholysis in housewives [133]; symptoms appeared after 2 weeks of using an enzyme detergent for approximately an hour each day without gloves. Patch tests with 1% and 2% aqueous solutions of the detergent were negative.

Figure 18.20 Discoloration of the digits and nails with edematous changes, due to solution used to give patina to belt buckles.Courtesy of X. Balguerie.

Figure 18.21 Nail discoloration and onycholysis due to 5% dinitro-orthocresol.

Prolonged occupational contact with formaldehyde solutions can cause softening and brown discoloration of the nail plate [134]. Formalin (37–50% solution of formaldehyde in water) is widely used industrially. It can be used as a preservative, a tanning agent, and to augment the water resistance of paper.

Gold potassium cyanide is responsible for a purplish-brown discoloration and onycholysis of the nails among electroplaters and electronics workers [135].

Hydrofluoric acid especially damages the subungual tissues, which are a common portal of entry for this highly destructive chemical (Fig. 18.23). The acid readily diffuses through minute holes in rubber gloves. Frequently the burn is unrecognized until up to 24 h later when excruciating pain begins; severe progressive tissue destruction results from the unique properties of the fluoride ion. The subungual tissues are especially susceptible to its destructive effect [136] and specific treatment with a topical 2% calcium gluconate preparation is indicated [137, 138] or, even better, intraarterial injection with a bolus of calcium (14 mg/kg) followed by prophylactic nail avulsion and continuous topical calcium gluconate therapy for 4–6 days [139]. Hydrofluoric acid is widely used in the semiconductor industry but can be a component of rust-removing agents [140, 141]. It is used, considerably diluted, to remove rust stains from fabrics prior to laundering and dry cleaning. It is also used in the manufacture of plastics, germicides, dyes, tanning solutions, solvents, and fireproofing materials; the glazing of pottery; photography; metal electropolishing; graphite processing; cleaning brick, stone, iron, and steel; and in the brewing of beer to control fermentation and to cleanse rubber pipes.

Organic solvents (Fig. 18.24) and motor oils (Fig. 18.25) also soften the nail plate and may produce koilonychia.

Oxalic acid, which is used in bleaching animal and vegetable materials, can cause redness and swelling of the fingertips together with a bluish discoloration and brittleness of the nails [142].

Figure 18.22 Yellow nails in a dinobuton handler. Courtesy of J.E. Wahlberg.
Bacterial infections

Abrasions and lacerations can cause problems. Even trivial breaks of the periungual skin may lead to more serious conditions such as cellulitis, erysipelas, and septicemia. The usual microorganisms are coagulase-positive staphylococci and various streptococci.

Pseudomonas infection results in the cosmetically distressing green nail syndrome. Healthcare personnel with green nails may be a source of nosocomial infections [143]. An isocyanate-resin-induced onycholysis with secondary Pseudomonas infection was held responsible for the occurrence of dark-green nails in a chemical mixer [144].

Paronychial infections are common and usually caused by a mixture of pathogenic organisms. Kitchen employees, agricultural workers, and pianists are particularly likely to develop this condition. Acute paronychia is frequently seen in meat handlers and streptococcal paronychia has been reported in workers in a chicken factory [145].

Inoculation through the periungual tissues of the spores of Clostridium tetani, which are widespread in soil, may lead to a full-blown tetanus infection.

Erysipeloid, fish handler’s disease, is a bacterial infection. The causative organism, Erysipelothrix rhusiopathiae, infests saltwater fish, shellfish, meat, and poultry. Therefore, at-risk occupations include fishermen, butchers, and poultry dressers. Breaks in the periungual area provide a portal of entry, although the bacterium can penetrate intact skin. Erysipeloid is a mild subacute cellulitis that resembles erysipelas. It presents as a painful, purplish papule, with a slowly spreading, dusky erythema as the center clears, and with lymphadenitis which may be associated with paronychia. Septicemia may occur.

Erysipeloid resolves spontaneously or with antibiotic therapy (penicillin).

Erysipeloid must be differentiated from “seal finger” which occurs in aquarium workers and veterinarians following trauma associated with working with seals. Zahaff et al. [146] described a case of leishmaniasis mimicking erysipeloid (Fig. 18.26).

Prosector’s paronychia is a primary inoculation infection with Mycobacterium tuberculosis (Fig. 18.27). Prosector’s wart (tuberculosis verrucosa cutis, verrucosa necrogenica) signifies a reinoculation of cutaneous tuberculosis (Fig. 18.28) more often than a primary inoculation infection. Infection usually occurs at an autopsy on a tuberculotic cadaver and it may occasionally be seen in pathologists, morgue attendants, and other hospital personnel [147–150]. Penetrating trauma is necessary for the initiation of the infection because the tubercle bacillus cannot traverse the normal skin barrier. Such primary inoculation tuberculosis is associated with a negative tuberculin test prior to infection,
 cf. reinoculation cutaneous tuberculosis; the differential diagnosis includes chancriform conditions of deep fungal or bacterial origin [151].

*Mycobacterium marinum* infection (*swimming pool granuloma*) gives rise to a slightly tender papule that develops at the proximal nail fold, which becomes pustular and drains. The drainage ceases within a week but the papule persists, gradually increasing in size (Fig. 18.29). The dorsal surface of the distal phalanx of the finger appears erythematous and verrucous [152]. The differential diagnosis includes atypical mycobacterial

---

**Figure 18.25** (a) Motor mechanic's fingers after prolonged handling of oil. (b,c) Onycholysis and subungual thickening due to mineral oils.

**Figure 18.26** Leishmaniasis mimicking erysipeloid, usually seen in meat or fish handlers. Courtesy of A. Zahaff.

**Figure 18.27** TB infection: primary (prosector's paronychia). Courtesy of D. Geoette.
infection, sporotrichosis, and tuberculosis verrucosa cutis. Frequently, swimming pool granuloma is a self-limited infection that may last for several months. Small lesions may be satisfactorily excised [153]. However, if the infectious material is not completely eradicated, relapse can be expected. Tetracycline in doses ranging from 1 to 2 g/day (or minocycline 100 mg bid) should be considered the treatment of choice in swimming pool granuloma.

Tularemia results from infection with the coccobacillus Pasteurella tularensis. Infection around the nail may be transmitted to humans by direct contact with infected wildlife (rabbits are the principal reservoirs of tularemia in nature). However, most infections are due to contact with animal carcasses [154]. Ulceroglandular tularemia (Fig. 18.30), the most common form, consists of a primary papule which becomes ulcerated, suppurative, and granulomatous at the site of inoculation, with regional lymphadenitis (bubonic tularemia). Over half the patients with cutaneous ulcers present with multiple lesions, including shallow erosions into the subungual tissues [155]. Streptomycin is generally the drug of choice but chloramphenicol, gentamicin, and tetracycline are also used in the treatment of tularemia.

Primary syphilis may be acquired occupationally, for example by doctors.

Viral infections

The orf virus infects sheep, goats, and even reindeer in and around the mouth and can be transmitted to man. The lesion in humans is most commonly on the dorsum
of the right index finger [156] (Fig. 18.31), and it can take on a target-like appearance. Spontaneous healing occurs, leaving a small scar [157]. Examination of an aspirate by electron microscopy confirms the diagnosis. The lesion resolves spontaneously within 6 weeks [158].

**Milker’s nodule** is a clinically similar viral infection (Fig. 18.32) caused by a paravaccinia virus and afflicts mostly agricultural workers and veterinarians. Viral cultures permit differentiation from orf. This condition passes through the same clinical sequence as orf, in appearance and timing, and heals spontaneously in 21–70 days without scarring [159]. Orf and milker’s nodule infection have distinctive histopathological features, and viral changes may frequently be found [160].

In “farmyard pox” Shelley and Shelley [161] recommend a less conservative attitude, suggesting its complete removal by epidermal subsection using a Gillette “Super blue” blade. Curettage followed by cautery was carried out in cases reported from North Jutland [162].

**Herpes simplex** infection is an occupational hazard of dentists [163], nurses [164], surgeons and anesthetists [165], and pathologists [166]. The eruption may resemble pyogenic paronychia to some extent, but the presence of several closely grouped vesicles on an erythematous base should suggest the diagnosis [167]. Two or more fingers may be involved at the same time.

**Viral warts** are more common in butchers [168–170]. Zerboni et al. [171] studied the prevalence of warts among the employees of a butchery: 29.7% in the butchers themselves, 11.8% in the meat packers, and 2.7% in the office staff. Viral warts are also common in poultry handlers [172], poultry processing workers [173], and fish handlers [174], in whom many of the lesions are periungual or subungual.

**Fungal infections**

Fungal infections of the nails and periungual region are common occupational problems (Box 18.1), particularly **candidiasis**. Those with occupations requiring the hands to be wet or exposed to detergents for prolonged periods, such as dishwashers in restaurants, are prone to candidal paronychia and onycholysis. **Candida** infections are also often seen in poultry and fish handlers.

Dermatophytic toenail infections are known to occur with increased prevalence in coal miners and colleagues who work in hot humid environments and who share washing facilities. Infection with *Trichophyton rubrum* often involves both feet and only one hand. Either hand may be involved [175]. A useful diagnostic feature of fungal nail involvement is the sparing of one or more nails, as opposed to psoriatic nail involvement where all the nails tend to be affected.

Alkiewicz and Sowinski [176] noted two cases of *Trichophyton* infection of the fingernails in a cashier and a teacher; their occupations required moistening of the tips of the fingers continually with a wet sponge. Fungal infections of the toenails have been reported in 6.5–27% of miners [177, 178], often associated with

**Box 18.1. Individuals at risk of fungal infections**

- Armed forces, police
- Athletes
- Dustmen
- Carpet weavers
- Employees of indoor swimming pools
- Excavation workers
- Mine workers
- Nuclear fuel workers
- Rubber industry workers
- Sewer workers
- Steel and furnace workers
- Wood cutters
- Wood pulp workers
Neoscytalidium dimidiatum and Neoscytalidium hyalinum [179]. Onychomycosis and keratomycosis were caused by Alternaria spp. in a wood pulp worker on chronic steroid therapy [180]. Green tea leaf pluckers may be affected by onychomycosis due to Neoscytalidium dimidiatum [181].

Primary cutaneous blastomycosis (Fig. 18.33) can be an occupational hazard to pathologists [182]. A reddish-purple furuncle of the distal part of the finger presents 2 weeks after accidental inoculation into a deep cut in the same area.

Systemic conditions

Besides chemical percutaneous absorption, which may be responsible for methemoglobinemia, systemic conditions, such as neurological and gastrointestinal symptoms related to patch tests with ultraviolet curable acrylic monomers and even death [183], may be due to chemical absorption by the inhalation route. After exposure to cobalt and tungsten [184], asbestos [185], talc, beryllium, and silica [6], pneumoconiotic lung diseases can produce clubbing. Dental technicians exposed to silica may present with Erasmus syndrome [186, 187].

Pseudoclubbing with acroosteolysis may develop after occupational exposure to excessive levels of vinyl chloride monomer which is responsible for systemic sclerosis [188]. Systemic sclerosis may also be caused by epoxy resin vapor, trichloroethylene, trichloroethane, and silica [189].

Davies et al. [190] reported on a cutaneous hemangi-endothelioma which developed on a toenail bed of a patient who had worked with polyvinyl chloride. Sclerodactyly with nail fold capillary changes, Raynaud phenomenon, and acroosteolysis [190–192] may also result from exposure to vibrations [193].

Lupus erythematosus-like erythema and periungual telangiectasia among coffee plantation workers have been reported [194].

Principal nail dystrophies associated with their occupational origin

Tables 18.1 and 18.2 and Boxes 18.2–18.7 demonstrate the principal nail dystrophies found in occupational nail disorders, but there are few correlations between clinical patterns and etiology [5].

Nail dyschromia indicates an abnormality in color of the fabric and/or surface of the nail plate and/or subungual tissue. Abnormalities of color depend on the transparency of the nail, its attachment to the underlying tissue, and the character of the latter.

Examination of the abnormal nails should be carried out with the fingers completely relaxed and not pressed against any surface. Then, the fingertips should be blanched to see if the pigmented abnormality is grossly altered; this may help to differentiate between discoloration of the nail plate itself and discoloration of the vascular nail bed. If the abnormality lies in the latter, it usually disappears.

Further information may be gleaned by transillumination of the nail. The modifications observed are differentiated readily from the diffuse homogeneous reddish glow of the normal nail plate [195]. If the discoloration is in the subungual soft tissues, its exact position can more easily be identified.

When discoloration results from abnormalities at the nail plate–nail bed attachment, leading to onycholysis and/or subungual hyperkeratosis, the history of the condition will help in diagnosis. Chemicals, wet occupation, trauma, or infection may be implicated. Thus, the history of the condition may, for example, confirm the traumatic origin of a hematoma. However, the possibility of malignant melanoma following trauma to a nail as a coincidental or causal event should be kept in mind [196].

When the pigmentation involves all the digits, it results from systemic absorption of a chemical.

- When the route of systemic absorption is oral, the discoloration is more likely to correspond to the shape of the lunula. Transverse leukonychia might occur, for example, in thallium poisoning.
Table 18.1 Nail plate color alterations.

<table>
<thead>
<tr>
<th>Sign</th>
<th>Workers affected</th>
</tr>
</thead>
<tbody>
<tr>
<td>Leukonychia</td>
<td>Arsenic workers</td>
</tr>
<tr>
<td></td>
<td>Butchers (Fig. 18.34)</td>
</tr>
<tr>
<td></td>
<td>Key punchers</td>
</tr>
<tr>
<td></td>
<td>Salt plant workers and contact with salted intestines (see Fig. 18.34)</td>
</tr>
<tr>
<td></td>
<td>Weedkillers (parquat)</td>
</tr>
<tr>
<td></td>
<td>Workers manufacturing thallium rodenticides</td>
</tr>
<tr>
<td></td>
<td>Fly tyer’s finger (apparent leukonychia)</td>
</tr>
<tr>
<td>Blue</td>
<td>Anodizers (aluminum)</td>
</tr>
<tr>
<td></td>
<td>Local argyria</td>
</tr>
<tr>
<td></td>
<td>Car mechanics (oxalic acid in radiators)</td>
</tr>
<tr>
<td></td>
<td>Cyanosis from methemoglobinemia or sulfhemoglobinemia</td>
</tr>
<tr>
<td></td>
<td>Dye makers</td>
</tr>
<tr>
<td></td>
<td>Electroplaters</td>
</tr>
<tr>
<td></td>
<td>Gold platers</td>
</tr>
<tr>
<td></td>
<td>Metal cleaners, metal patina solution</td>
</tr>
<tr>
<td></td>
<td>Ink makers</td>
</tr>
<tr>
<td></td>
<td>Paint removers</td>
</tr>
<tr>
<td></td>
<td>Photographers</td>
</tr>
<tr>
<td></td>
<td>Rust removers</td>
</tr>
<tr>
<td></td>
<td>Silver workers (presenting generalized argyria)</td>
</tr>
<tr>
<td></td>
<td>Textile workers</td>
</tr>
<tr>
<td>Brown/black</td>
<td>Cigar makers</td>
</tr>
<tr>
<td></td>
<td>Cobblers</td>
</tr>
<tr>
<td></td>
<td>Coffee bean workers</td>
</tr>
<tr>
<td></td>
<td>Cooks and bakers (burnt sugar)</td>
</tr>
<tr>
<td></td>
<td>Electric bulb cleaners (hydrochloric acid)</td>
</tr>
<tr>
<td></td>
<td>Gunsmiths</td>
</tr>
<tr>
<td></td>
<td>Hairdressers (Fig. 18.35)</td>
</tr>
<tr>
<td></td>
<td>Pecan nut pickers</td>
</tr>
<tr>
<td></td>
<td>Photographers</td>
</tr>
<tr>
<td></td>
<td>Roadway pavers</td>
</tr>
<tr>
<td></td>
<td>Shoe shiners</td>
</tr>
<tr>
<td></td>
<td>Vintners (red wine)</td>
</tr>
<tr>
<td></td>
<td>Walnut pickers (pecans) (Fig. 18.36)</td>
</tr>
<tr>
<td></td>
<td>Wood workers (ebony, mahogany)</td>
</tr>
<tr>
<td></td>
<td>Wood workers (varnish)</td>
</tr>
<tr>
<td></td>
<td>Bartenders</td>
</tr>
<tr>
<td></td>
<td>Dish washers</td>
</tr>
<tr>
<td></td>
<td>Electricians</td>
</tr>
<tr>
<td></td>
<td>Fruit handlers</td>
</tr>
<tr>
<td></td>
<td>Laundry workers</td>
</tr>
<tr>
<td></td>
<td>Metallurgists</td>
</tr>
<tr>
<td></td>
<td>Restaurant workers</td>
</tr>
<tr>
<td></td>
<td>Sugar factory workers</td>
</tr>
<tr>
<td></td>
<td>Yellow</td>
</tr>
<tr>
<td></td>
<td>Epoxy system handlers: methenylene diamine and 4,4′-methylene diamine (Fig. 18.37)</td>
</tr>
<tr>
<td></td>
<td>Flower handlers</td>
</tr>
<tr>
<td></td>
<td>Pesticide workers: diquat, paraquat, dinitro-orthocresol, dinobuton</td>
</tr>
<tr>
<td></td>
<td>Workers handling chromium salts</td>
</tr>
<tr>
<td></td>
<td>Workers handling dyestuffs: dinitro-salicylic acid, dinitrobenzene, dinitrotoluene</td>
</tr>
</tbody>
</table>

Table 18.1 (Continued)

<table>
<thead>
<tr>
<th>Sign</th>
<th>Workers affected</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Fruit handlers</td>
</tr>
<tr>
<td></td>
<td>Laundry workers</td>
</tr>
<tr>
<td></td>
<td>Metallurgists</td>
</tr>
<tr>
<td></td>
<td>Restaurant workers</td>
</tr>
<tr>
<td></td>
<td>Sugar factory workers</td>
</tr>
<tr>
<td></td>
<td>Yellow</td>
</tr>
<tr>
<td></td>
<td>Epoxy system handlers: methenylene diamine and 4,4′-methylene diamine (Fig. 18.37)</td>
</tr>
<tr>
<td></td>
<td>Flower handlers</td>
</tr>
<tr>
<td></td>
<td>Pesticide workers: diquat, paraquat, dinitro-orthocresol, dinobuton</td>
</tr>
<tr>
<td></td>
<td>Workers handling chromium salts</td>
</tr>
<tr>
<td></td>
<td>Workers handling dyestuffs: dinitro-salicylic acid, dinitrobenzene, dinitrotoluene</td>
</tr>
</tbody>
</table>

Figure 18.34 Butcher’s leukonychia. Courtesy of F. Leu.

Figure 18.35 Brown discoloration of nails in a hairdresser due to a dye.
When systemic absorption of a chemical through the lung or the skin produces dyschromia, there are two possibilities. Disappearance of the pigmentation on the nail bed blanching test means that the pigment originates from the blood vessels. Methemoglobinemia, as an example, manifests as a bluish discoloration of the terminal digits and should be looked for in an otherwise asymptomatic worker, i.e. following exposure to:

- Asbestos
- Talc
- Beryllium
- Silica
- Cobalt
- Tungsten
- Vinyl chloride monomer
- Polyvinyl chloride
- Vinyl chloride monomer
- Epoxy resin (vapors)
- Trichlorethylene, trichlorethane
- Silica
- Vibrations
- Coffee (in plantation workers)

### Table 18.2 Clubbing and pseudoclubbing.

<table>
<thead>
<tr>
<th>Clinical sign</th>
<th>Exposure to:</th>
</tr>
</thead>
<tbody>
<tr>
<td>Clubbing (resulting from pneumoconiotic lung diseases)</td>
<td>Asbestos, Talc, Beryllium, Silica, Cobalt, Tungsten</td>
</tr>
<tr>
<td>Pseudoclubbing (systemic sclerosis with acroosteolysis) (Fig. 18.38)</td>
<td>Vinyl chloride monomer</td>
</tr>
<tr>
<td>Cutaneous hemangioendothelioma</td>
<td>Polyvinyl chloride</td>
</tr>
<tr>
<td>Collagen diseases</td>
<td></td>
</tr>
<tr>
<td>Systemic sclerosis</td>
<td>Vinyl chloride monomer, Epoxy resin (vapors), Trichlorethylene, trichlorethane, Silica, Vibrations</td>
</tr>
<tr>
<td>Sclerodactyly associated with nail fold capillary changes, Raynaud phenomenon, acroosteolysis</td>
<td></td>
</tr>
<tr>
<td>Lupus erythematosus-like erythema and periungual telangiectasia</td>
<td>Coffee (in plantation workers)</td>
</tr>
</tbody>
</table>

- When systemic absorption of a chemical through the lung or the skin produces dyschromia, there are two possibilities.
  - Disappearance of the pigmentation on the nail bed blanching test means that the pigment originates from the blood vessels. Methemoglobinemia, as an example, manifests as a bluish discoloration of the terminal digits and should be looked for in an otherwise asymptomatic worker, i.e. following exposure.
Box 18.2 Individuals at risk of nail fragility syndrome resulting from repeated microtrauma. This syndrome leads to a gradual destruction of the nail plate, which becomes brittle and atrophic. Nail fragility may occur in isolation or be associated with paronychia and/or onycholysis (see parentheses for other presenting features)

- Bean shellers and potato peelers (paronychia)
- Butchers
- Cement workers
- Chemists and laboratory workers (paronychia)
- Dentists (onycholysis, subungual hyperkeratosis, dermatitis)
- Engravers (paronychia)
- Etchers (paronychia)
- File makers
- Glaziers (paronychia)
- Hat cleaners (paronychia)
- Nurses
- Optical glass handlers
- Packers
- Painters (paronychia)
- Photographers (paronychia, discoloration)
- Plasterers (corroded nails)
- Porcelain workers (serrated nails)
- Pottery workers
- Radio workers (paronychia and nail loss)
- Rope workers
- Shoe makers (onycholysis and paronychia)
- Shoe shiners
- Silk weavers
- Tailors
- Tea-pickers
- Weeder’s thumb (hematoma)
- Wet work (paronychia)
- Wood workers (paronychia and stains)
- Workers exposed to microwave radiation (onycholysis)
- Workers handling small instruments
- Workers repeatedly lifting heavy plastic bags

Box 18.3 Toenail dystrophy resulting from repeated microtrauma

- Dancers (exostosis)
- Miners (onychomycosis)
- Rickshaw pullers (koilonychia)
- Sportsmen (hematoma, nail shedding): athletes, joggers, walkers, squash players, soccer players, tennis players

Box 18.4 Occupational paronychia

- Agricultural workers
- Animal origin (bristles, sea urchin, oyster shell)
- Automotive workers (sulfuric acid exposure from batteries)
- Bakers and pastry cooks
- Barbers and hairdressers (onycholysis)
- Bartenders
- Bean shellers
- Book binders (paste)
- Bricklayers (limes, cement, mortar)
- Builders and carpenters (including glass fiber)
- Button makers
- Cement workers
- Chemists and laboratory workers
- Chicken factory workers
- Confectioners
- Cooks
- Cosmetic workers
- Dentists
- Dinitro-salicylic acid
- Dyers (aniline dyes, producing stains and necrosis)
- Engravers (brittle nail)
- Etchers, glass etchers (brittle nail)
- Fishermen
- Fishmongers
- Florists and gardeners (onycholysis) (hyacinth, daffodil, and narcissus bulbs, tulip fingers)
- Glaziers (brittle nail)
- Groundskeepers
- Harpists
- Housewives/husbands and house cleaners
- Janitorial and domestic workers
- Manicurists (artificial nails)
- Meat handlers
- Mechanics
- Milkers (onycholysis from bristle)
- Oil rig workers
- Painters
- Pathologists
- Photographic developers (brittle nail, discoloration)
- Pianists
- Physicians, dentists, nurses
- Potato peelers
- Prosector’s paronychia
- Radio workers (methanol, causing pigmentation and nail loss)
- Salt plant workers (ulcers)
- Shoe workers (brittle nails)
- Swimming pool granuloma
- Tanners (whitlow)
- Textile workers (threads of fabric)
- Violinists (nail dystrophy)
- Wood workers (brittle nails, stains)
- Wool workers (wool thread)
to aromatic nitro and amino compounds that can penetrate all glove materials. The color disappears within 16 h of leaving work, in contrast to sulfhemoglobinemia which presents with the same distal discoloration as an early warning sign of intoxication but which disappears only with the normal life span of the red blood cell, i.e. 4 months [6]. Deaths from asphyxia among fishermen have been reported [183]. The workers had previously been involved in dipping shrimps into a sodium bisulfite solution used routinely to control “black spots,” a discoloration associated with decay. A fungicide, zinc ethylene bisdithiocarbamate, was also responsible for sulfhemoglobinemia and acute hemolytic anemia in a patient with glucose-6-phosphate dehydrogenase deficiency and hypocatalasemia [197].

- If the pigmentation is not altered on the nail bed blanching test but is obliterated by the pen-torch pressed against the pulp, then the pigment is deposited in the nail bed tissue, as observed in the blue nails of silver refinery workers [198].

However, the distinction between oral absorption and systemic absorption of the chemical through the lung or the skin is not clear cut. For example, occupational exposure to polychlorinated biphenyls (PCBs) is usually through direct contact, but inhalation and ingestion may also be operative in some cases. Discoloration of the nails appeared in 2.5% of PCB-exposed capacitor manufacturing workers [199].

Non-occupational nail hazards

There are few direct hazards to the nails that are not occupational and these very largely consist of cosmetic applications to the nails. Nail preparations rarely damage
the nails themselves. When they do, their effect is usually quickly perceived and the product either radically altered or withdrawn from the market.

The principles of diagnosis of these rare non-occupational but exogenous nail disorders are the same as those for occupational nail disorders outlined under “Diagnosis of occupational nail disorders.” Besides the cosmetic hazards that are specified in this section, there are several conditions described previously that can sometimes also arise non-occupationally from leisure pursuits, e.g. “do-it-yourself” activities and housework. These are not repeated here. Allergic contact dermatitis from acrylic sculptured nails has been included earlier because of its occurrence in manicurists as well as in their clients. Permanent loss of fingernails due to allergic reaction to an acrylic nail preparation seems unique [200]. The use of cyanoacrylate nail glue preparations may produce allergic reactions in the nail plate and paronychial area, which may be prolonged with resultant marked dystrophy of the nails [201] and even partial loss that may eventually prove permanent.

**Cosmetic physical hazards**

A variant of worn-down nail, the so-called “bidet nail,” was described in women excessively concerned about hygiene. The defect involved the middle three fingernails of the dominant hand. The dystrophy was triangular with its base lying at the free edge of the nails where the thinning was proximal [202]. See also Chapter 2. A similar dystrophy has been described in children [22] and in adult males [203].

**Cosmetic chemical sensitizers or irritants**

See Chapter 19.

**Discoloration of the nail plate**

See Chapters 2 and 19.

**Systemic absorption of a chemical**

There are some drugs that produce systemically lichenoid reactions such as salsalate, a non-steroidal antiinflammatory drug [204]. In other cases brimonidine [205], eye drops against glaucoma, and amalgam dental filling with mercury were responsible for typical cases of nail lichen planus [206, 207].

**Nail protection at work**

Gloves are the best form of such protection, but only if they are considered safe to wear and if they are made of material appropriate to the agent against which protection is required. Neither natural rubber nor polyvinyl chloride (PVC) gloves, for example, provide good protection against organic solvents. Further general guidance is given in Table 18.3. Expert detailed advice is now available [208, 209].

**Nail cosmetic hazards at work**

Can it definitively be proved that artificial nails or even nail varnish present absolutely no risk of spreading bacteria? In 1982 Nava [210], a researcher, noted that polished nails pose no infection problem as long as they are manicured and have no chips or cracks, a statement confirmed by Baumgardner et al. [211]: nail polish worn on short, healthy nails does not appear to be associated with increased microbial counts on the fingernails. However, this contradicts a previous statement that nail polish and rings make hands difficult to decontaminate [212] and “recommended practices preclude artificial nails” [213]. It has been shown that chipped fingernail polish or fingernail polish worn longer than 4 days fosters increased numbers of bacteria on the fingernails of operating room nurses after surgical hand scrubs [214]. After hand washing, higher numbers of colony-forming units of gram-negative rods were cultured from the fingertips of nurses with artificial nails than from those of nurses with natural nails. Because of the number of nosocomial infections caused by gram-negative rods, healthcare workers who wear artificial nails should consider the potential risk of increased carriage of gram-negative rods [215]. Certain genera of bacteria, for example *Serratia, Acinetobacter*, and *Pseudomonas*, were recovered only from nurses with artificial nails.

Anecdotal reports from North America have also suggested that nurses who wear acrylic fingernails may become colonized or infected by *Candida* and, thus, become a possible risk to susceptible patients. This possibility remains to be established in clinical practice, though there are theoretical reasons for concern, notably

**Box 18.7 Distal bone anomaly**

- Acroosteolysis
- Acute injury
- Dancers
- Erasmus syndrome
- Exposure to vibrations
- Fracture of the distal phalanx
- Guitar players
- Necrosis of the digits
- Pseudoclubbing with acroosteolysis (Fig. 18.38a)
- Sclerodactyly with acroosteolysis
- Subungual exostosis
- Vinyl chloride monomer
the capacity of *Candida* to adhere to acrylic surfaces, as recognized in denture stomatitis [216].

Three case reports of *Pseudomonas* corneal ulcers following injury to the eye with artificial nails have been published [217]. If transmission occurs on one individual, there is no reason why it cannot occur from one person to another [218].

The Association of Operating Room Nurses (AORN) recommends that artificial nails are not worn by operating room personnel, citing reports of fungal and bacterial infections. In addition, concerns have also been raised by others that the use of artificial fingernails and nail polish may discourage vigorous hand-washing [219]. Therefore, many hospitals have adopted the AORN’s guidelines and some have extended them beyond the operating room, for example in prohibiting nurses who work in the neonatal intensive care and labor and delivery units from wearing artificial nails [220].

Some food-processing plants have also banned artificial nails and nail polish, because they cannot let anything fall into the “food stream.” A number of occupations and companies now have policies regarding the maintenance and appearance of their employees’ nails.

**Table 18.3 General guidance on glove materials.**

<table>
<thead>
<tr>
<th>Material</th>
<th>Protective against</th>
<th>Additional notes</th>
</tr>
</thead>
<tbody>
<tr>
<td>Natural rubber</td>
<td>Soaps and detergents, water-soluble irritants, dilute acids and alkalis</td>
<td>Not good for organic solvents, strong acids and alkalis, many other organic compounds</td>
</tr>
<tr>
<td>Butyl rubber</td>
<td>Aldehydes, most amines, amides, ketones, formaldehyde</td>
<td>Not good for resins, epoxy resins, most acrylates, isocyanates</td>
</tr>
<tr>
<td>Chloroprene</td>
<td>Soaps and detergents, dilute acids and alkalis, certain amines and esters, most alcohols, vegetable oils</td>
<td>Not good for aldehydes, ketones, nitro- and halogenated compounds</td>
</tr>
<tr>
<td>Fluorocarbon</td>
<td>Organic solvents, particularly halogenated and aromatic hydrocarbons</td>
<td>Cost 30–40 times as much as natural rubber</td>
</tr>
<tr>
<td>Nitrile rubber</td>
<td>Organic acids, certain alcohols, amines, ethers, peroxides, inorganic alkalis, vegetable oils</td>
<td>Also protect against organophosphorus compounds to some extent</td>
</tr>
<tr>
<td>Styrene–butadiene rubber</td>
<td></td>
<td>Hypoallergenic surgical gloves only</td>
</tr>
<tr>
<td>Polyethylene</td>
<td>Mainly for food handlers and medical personnel</td>
<td>Chemical resistance dependent on seams</td>
</tr>
<tr>
<td>Polyvinyl alcohol</td>
<td>Several organic solvents, most esters</td>
<td>Not resistant to water or aqueous solutions</td>
</tr>
<tr>
<td>Polyvinyl chloride</td>
<td>Soaps and detergents, oils, metal-working fluids, dilute acids and alkalis, vegetable oils</td>
<td>Not good for most organic solvents</td>
</tr>
</tbody>
</table>

*Actual protection depends on glove thickness, manufacturing quality, chemical concentration, duration of contact, environmental temperature and humidity, etc.*

References

61 Fulghum DD. (1972). Allergic contact onycholysis due to poison ivy oleoresin. Contact Dermatitis Newsletter. 11: 266.
Chapter 18


199 Fischbein A, Wolf MS, Lilis R et al. (1979). Clinical findings among PCB-exposed capacitor


The art of nail care

Both women and men have long shown great interest in the care and adornment of the natural nail plate. The human nail plate has a wide variety of physical characteristics, primarily differing in color, thickness, contour, length, flexibility, surface smoothness, and durability. The nail plate is chemically similar to animal horn, hoof, and claws and provides many important functions including more efficient use of the fingers, hands, toes, and feet, as well as improved dexterity and protection for delicate distal phalanges. Since the nail plate is often associated with harboring or transferring microorganisms, toxins, irritants, and allergens, it is essential to maintain cleanliness.

Many implements, tools, products, and services have been developed to enhance the attractiveness, improve the condition, and maintain health of the nail unit as a whole. This innate desire existed in many ancient societies where nail beautification was an established practice [1]. The long fingernail, often accentuated with gold and jeweled fingertip extenders, was indicative of high rank and station in society. Coloring or staining the nail plate has been the practice throughout the ages and basic nail grooming is practiced universally and not limited to women. Both sexes associate nail grooming with cleanliness and improvement in confidence and self-image, so physicians are well advised to recognize that the patient’s nail appearance and condition can often provide a psychological boost. This great benefit dwarfs to insignificance the already relatively low risks of developing adverse skin reactions, of which most are preventable, as will be discussed in this chapter.

In its most basic form, nail care requires only liquid soap, water, and a clean brush to assist removal of oils, debris, and microorganisms from under the extended edge of the nail plate and in the lateral nail folds. Table 19.1 provides a brief description of the implements used to manicure the nail (Figs 19.1–19.3).

Basic manicure

The following is a list of steps taken to perform a basic manicure. An individual at home will often shorten or completely omit some steps due to time constraints and/or dexterity. Physicians should be familiar with these procedures, especially since, incorrectly performed, manicuring may lead to ungual and periungual problems, including infection.

An attractive fingernail is oval in shape but there are three other basic nail shapes: round, rectangular, and pointed. Length creates the impression of thin, tapered,
and graceful fingers (Fig. 19.4). Excessive length, however, interferes with the efficiency of the hand’s performance (Fig. 19.5).

Steps of a basic manicure

See Figure 19.6.

1) Surface oils or other contaminants, including microorganisms, are removed by thoroughly scrubbing the hands with liquid soap, running water, and a clean/disinfected soft-bristled nail brush.

2) Preexisting nail polish is thoroughly removed with a cotton ball or more preferably plastic-backed pads saturated with nail polish remover, usually acetone or ethyl acetate, which is sometimes diluted with water to reduce drying of the skin.

3) The nail plates are shaped with an abrasive file. Usually a 180-grit file is used to shorten and shape the nail plate, since lower grit abrasive files are too aggressive and may promote nail plate fracturing or surface peeling.
4) The dorsal surface of the nail plate is gently smoothed with an abrasive file, usually 240 grit or higher (finer grit), to prevent excessive thinning of the nail plate.

5) The fingertips are then soaked in a bath of warm, soapy water for several minutes to allow the distal edge of the proximal nail fold to soften and allow it to be gently pushed back to expose the lunula. This provides a more desirable oval-shaped appearance to the nail plate. This desired final appearance will only be achieved after a number of treatments of this type over several weeks, to prevent damaging the barrier seals which protect the matrix from potential infection. Aggressively overmanicuring the distal proximal nail fold may also result in the appearance of multiple transverse ridges.

6) Alkaline-based cuticle remover (typically pH 12–14) or natural oils such as jojoba, rice bran, and sweet almond are then applied to the exposed nail plate, and after several minutes the pusher is used to gently scrape remnants of cuticle tissue adhering to the plate. This is necessary for good adhesion of any coatings applied to the nail plate, e.g. nail polish or artificial nails.

7) Loose, dead skin tags on the proximal nail fold are carefully cut away, without ripping, with a sharp pair of nippers. In a professional salon environment, nippers should never be used to cut hardened skin from the dorsal proximal nail fold. Nail professionals are not licensed to cut living skin and this potentially

Figure 19.3 Pusher.

Figure 19.4 Showing the esthetic difference between long red nails and uncolored ones (same individual).

Figure 19.5 “Lever” effect of long nails, which may lead to onycholysis. Excessively long nails may interfere with the subtle functions of the hands.
harmful practice increases the risk of infection. Many often confuse this hardened tissue for the cuticle.

8) The nail plate should be cleansed again with nail polish remover to eliminate surface dusts/residues and buffed with a 1200–2400 grit abrasive file and nail oil to achieve a high-gloss shine, if it is desired that the natural nails be worn without nail polish. If nail polishes are to be worn, it is best not to overly smooth the nail plate or to use nail oils since both practices can adversely affect nail polish adhesion.

9) Nail polish provides gloss and decorative effects in a broad spectrum of colors and shades. Generally, two coats are required to achieve a smooth, attractive finish. Base coats are often applied first, to improve adhesion to the natural nail as well as to prevent surface staining from nail polish colorants, especially those with a red or reddish coloration. Application of a top coat over the nail polish increases gloss, prevents discoloration, and enhances wear characteristics.

10) Toenail care follows similar procedures. However, toenail plates should be clipped and filed to achieve almost a square or slightly oval free edge carried just beyond the toe, in order not to interfere with the pressure of footwear, and to avoid an ingrown nail. It is easier to groom toenails if cotton strips are placed between the digits.

Special products and procedures

Waterless manicure

Due to increased concerns over the adverse effects of water on the natural nail plate, many now avoid soaking nail plates in water and skip over Step 5. Soaking for up to 5 min in warm soapy water allows enough water absorption to cause some nail plates to swell and change shape. As the excess water evaporates from the nail plate, it will revert to its original thickness and shape. This can stretch the nail coating and lead to a loss of adhesion causing the coating to peel from the plate. If the nail plate has preexisting cracks, breaks, or surface peeling, excessive water exposure can also aggravate and worsen these conditions.

Natural nail mending techniques

Depending on the strength and durability of the natural nail, it may be difficult to grow the nail plates beyond the fingertip without breaking. Minor splits or fractures to the free edge can be repaired by sticking a small piece of mending material (paper or fabric) to the damaged area with clear nail polish or base coat, after which colored enamel and a clear top coat/sealer may be applied (Fig. 19.7). This achieves acceptable cosmetic results and can help prevent the damage from worsening. Quick, efficient nail mending kits are available and usually contain paper or silk strips that are applied to the nail fracture with a cyanoacrylate glue and can even be used to temporarily repair a completely severed nail plate tip. If the adhesive is applied to the non-viable nail plate, the possibility of an allergic reaction is greatly minimized.

Advanced techniques utilizing cyanoacrylate adhesives require additional care and skill, since cyanoacrylate monomers harden quickly when exposed to any source of moisture and can instantly bond skin together, e.g. fingers or eyelids. Fingers are easily separated by immersion in acetone and patiently waiting for the adhesive to completely dissolve, usually 1–3 min. Accidental eye exposure is a very real risk which requires immediate medical attention for resolution. Safety eyewear should always be worn whenever cyanoacrylate monomer adhesives are in use.
Nail plate hardeners

Highly flexible nail plates pose difficulties to those desiring long tapered nails, since “flexing” can sometimes lead to the formation of stress cracks in the lateral side walls of the plate. Regular application of 1–2% formalin solutions will stiffen the nails, but with repeated application can lower flexibility/increase stiffness and reduce durability, which results in nail brittleness. Although considered unusual occurrences, local irritation, allergic dermatitis, pain, onycholysis, subungual hyperkeratosis, and even subungual hemorrhages have been reported [2]. In addition, prolonged use of nail hardeners containing formalin can cause already brittle nail plates to become increasingly brittle. Therefore, such products should be restricted for use on thin and/or overly flexible nail plates. Also, once the desired rigidity is obtained, discontinue use to prevent embrittling of the nail plate, and use only as needed.

It is a misconception that 37% formalin is 37% formaldehyde. This misunderstanding developed over 100 years ago when it was believed that formalin was “formaldehyde water,” since it was created by bubbling anhydrous formaldehyde gas through water. It is now known that 37% formalin actually contains only 0.0466% free formaldehyde (CAS#50-00-0/EINECS 200-001-8), since the vast majority of formaldehyde gas reacts with water to create methylene glycol (CAS#463-57-0/EINECS 207-339-5) (Fig. 19.8a–c).

Unfortunately, researchers around the world continue to believe this misconception and even some manufacturers of formalin perpetuate this myth. Even though methylene glycol and formaldehyde exist in equilibrium, the chemical equilibrium is shifted greatly toward methylene glycol, and in water-containing cosmetics methylene glycol is the predominant species and found in ratios of 99.6% methylene glycol to 0.04% formaldehyde [3]. This misconception has led regulators to assume incorrectly that methylene glycol and formaldehyde are synonyms, when in fact they are chemically, physically and structurally different, even belonging to separate chemical families, aldehyde versus alcohol. Common test methods for cosmetics often overreport the amount of free formaldehyde by more than 100 times, since these methods artificially force methylene glycol to convert into formaldehyde, which is trapped by derivatizing agents, e.g. 2,4-dinitrophenylhydrazine (DNPH), and then measured and reported as if it were free formaldehyde [4]. Even though European regulations require the reporting of “free formaldehyde,” the official testing methodologies actually measure and report both free formaldehyde (ppm levels) and methylene glycol (vast majority). The only known methods for accurately and reproducibly measuring methylene glycol and determining free formaldehyde levels in water-based cosmetic products involve the use of carbon-13 nuclear magnetic resonance [4, 5].

Another example of how this misconception has incorrectly skewed regulations is that the United States Food and Drug Administration (FDA) allows up to 5% formaldehyde in nail hardeners, which is an impossibly high amount for an anhydrous gas, so almost certainly its intent was to limit the amount of formalin liquid used and not formaldehyde gas. Regulations in Japan, Canada, and Europe also incorrectly referred to methylene glycol as though it were formaldehyde gas. This has become especially problematic since anhydrous formaldehyde gas is listed as a human carcinogen, whereas methylene glycol is not.

Nail wraps and dip systems

Nail wraps are professional salon services, which can be performed in several different ways utilizing various application techniques (Table 19.2). These artificial nail coatings (Fig. 19.9) are made by embedding a fibrous substance, typically thin layers of paper, silk, linen, or fiberglass, inside multiple layers of methyl or ethyl
cyanoacrylate monomer which are then hardened to the nail plate. The exception would be products marketed as “no light gels” which are thickened cyanoacrylate monomers that are applied to the nail plate as a protective coating, but without impregnating a fibrous substance.

Cyanoacrylates (CA) are highly sensitive monomers that will slowly polymerize and harden when exposed to traces of moisture, but harden instantly upon exposure to the fine mist of the spray-on “catalyst,” e.g. 1% N,N-dimethyl paratoluidine (DMPT) in a volatile solvent. The catalyst can also be applied to the embedded fabrics or can be sprinkled via coated powder spheres made from high-molecular-weight ethyl or methyl methacrylate polymers.

Cyanoacrylate monomer is applied directly from the container’s nozzle, which smooths it into place over the nail or fabric, and the catalyst is then applied. After 5–10 min, the nail wrap can be shaped and then buffed to a high shine, but most often nail polish is applied. As described previously, a version of this technique is used to mend nail plate tears by sticking a piece of fabric over the broken area. Depending on the skill and quality of workmanship, applying a full set of nail coatings using this method may require as much as 2 h to perform.

These nail coatings are highly susceptible to moisture and usually last 2–3 weeks, when the artificial nail is removed and reapplied. Nail wraps easily remove within 10 min after soaking in a nail wrap product remover, normally acetone blended with skin moisturizing ingredients to reduce the appearance of dry skin. Nail wrapping is no longer widely performed, but is expected to account for up to 2% of the worldwide market [6]. Nail wrapping has largely been replaced by simpler methods.

The more common alternative is to apply the cyanoacrylate adhesive to the nail plate and then dip the finger into methacrylate powders. The powder particles reinforce the coating, in the same way as does fabric or paper. These are the same powders used for other types of nail coatings, except they are not required to contain benzoyl peroxide as a polymerization initiator. Double-dipping clients’ fingers into the powder can lead to microbial contamination of the powder, therefore these powders should be disposed of after use and cross-contamination avoided. Alternatively, the powders can be sprinkled over the surface of the nail plate.
Contact sensitization to cyanoacrylate adhesive may result in severe onychodystrophy \([7–9]\) and dermatitis at remote sites \([10]\).

**Sculptured nails ("acrylic" nails)**

The original artificial nail enhancements were based on systems similar to orthodontic products which often utilized methacrylate monomers and polymers (Table 19.3).

Methacrylates are structurally different from acrylates, have different safety profiles, and should not be confused. A methacrylate (Fig. 19.10) possesses a branching methyl group \((-\text{CH}_3\)) attached to the double bond of ethyl methacrylate, making the molecule 10% larger and altering its shape, which potentially reduces skin penetration and may help explain why methacrylate monomers are less likely to cause adverse skin reactions when compared to homologous acrylate monomers, e.g. ethyl acrylate versus ethyl methacrylate. This is an important reason why artificial nails utilizing acrylates are more likely to cause adverse skin reactions than those based solely on methacrylate monomers or oligomers \([11]\).

Methacrylate monomer-based artificial nail systems remain among the most widely used artificial nails in the world. What is often called the “liquid” is far more complex than it sounds. These are sophisticated blends containing ethyl methacrylate \((60–95\%)\) and other di- or trifunctional methacrylate monomers \((3–5\%)\). Multifunctional cross-linking monomers improve durability and inhibitors such as hydroquinone \((100–1000 \text{ ppm})\) prevent premature polymerization and improve shelf-life. Ultraviolet (UV) stabilizers and catalysts such as dimethyltolylamine \((0.75–1.25\%)\) are also used, along with soluble colorants, flexibilizing plasticizers, adhesion promoters, and other additives. The second part of the system is called the “powder” and consists of fully polymerized methyl and/or ethyl methacrylate polymer beads \((~50–80\mu\text{m})\), coated with 1–2% benzoyl peroxide as the polymerization initiator, various colorants, opacifiers such as titanium dioxide, and other additives. When the benzoyl peroxide mixes with the precatalyzed monomer liquid, polymerization commences quickly at normal room temperatures, usually within 1–2 min.

These types of artificial nails are applied by dipping a brush into the monomer liquid, wiping off the excess on the inside lip of a low-volume \((3–5\text{ mL})\) container called a “dampen dish,” and then drawing a fine-tipped brush through the polymer powder to create slurry that forms a small bead attached to the end of the brush. Several beads are applied and smoothed into shape with the 180-grit abrasive file.

![Figure 19.9](Image)

**Figure 19.9** Professional supplies for applying nail wraps: (1) fiberglass; (2) cyanoacrylate monomer (resin); (3) spray-on catalyst. Courtesy of Paul Rollins Photography.

### Table 19.3

Overview of the so-called “liquid and powder” type of artificial nails.

<table>
<thead>
<tr>
<th>Commonly called</th>
<th>Other names</th>
<th>Typical catalyst</th>
<th>Chemistry</th>
</tr>
</thead>
<tbody>
<tr>
<td>Liquid and powder</td>
<td>Acrylic, porcelain</td>
<td>Methacrylate polymer powder treated with benzoyl peroxide. Liquid monomer contains tertiary aromatic amine</td>
<td>Methacrylate monomers and polymers</td>
</tr>
<tr>
<td></td>
<td>nails, solar nails</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

![Figure 19.10](Image)

**Figure 19.10** Structural differences between methacrylate and acrylate monomers.
or an electric file with a similar grit abrasive bit. Various shades of pink powders are used for application over the nail bed area, while white or off-white powders are used to simulate the extended edge of the nail plate. Although the slurry immediately begins to polymerize and will harden within 2–3 min, 95% of the polymerization occurs in the first 5–10 min and the remaining 5% may take 24–48 h to react [12]. After shaping, the finished nail can be buffed to a high shine or nail color applied.

Newer artificial nail formulations utilize monomers with significantly improved adhesion to the natural nail plate, so use of pretreatment factors called “primers” is now considered optional. There are several types of primers including acid primer (methacrylic acid) and non-acid primer (BIS-GMA methacrylate; Fig. 19.12) and proprietary UV-curing primer compositions composed of chemically similar materials. Artificial nail primers no longer utilize methacrylic acid since it may represent a corrosive hazard to young children and has led to severe injuries in the home [13].

To artificially extend the nail plate, a metalized paper-board template is first applied to the natural nail, before the liquid/powder slurry is applied (Fig. 19.13). Depending on the skill and quality of workmanship, 60–90 min is required to complete a full set. Each artificial nail must be refurbished (called rebalancing) every 2–3 weeks in order to make small repairs and fill in the area of new growth. Nail elongation is more commonly achieved by sticking a plastic preformed tip to the nail plate with CA monomer adhesive, then applying the liquid/powder slurry over the extension and allowing it to harden. Removal requires soaking for 30 min in acetone, but this type of artificial nail is usually only permanently removed; otherwise, they are maintained as previously described.

Methemoglobinemia has been reported from the ingestion of artificial nail solution [14]. Allergic contact-type inflammation of ungual and periungual areas, infection, foreign body reactions, hemorrhage, and severe pain have been reported; secondary nail dystrophy is not unusual [15–17] (Figs. 19.14–19.16). Fisher described a single case of persistent paresthesia and anonychia from the procedure 16 years previously [16, 17]. Since this publication, new cases of paresthesia have been reported [18, 19]. Baran and Schibli and then Fisher and Baran also observed a case of permanent paresthesia without anonychia and without sensitization to the acrylic monomer [20, 21]. Koppula et al. found that several acrylates are useful as screening patch test allergens [22].

Premixed acrylic gels (ultraviolet cured gels)

Certain types of artificial nail coatings cure under low-intensity UVA light, typically 435–325 nm, to create artificial nails which are called “UV gels” (Fig. 19.17). UVB and C are not used to create UV gel nails [23] (Table 19.4). Typically, clients’ hands are exposed for less than 10 min, twice a month. The measured level of exposure to UVA and B (with no exposure to UVC) has been determined to be low when compared to natural sunlight exposure, and receiving regular salon services is equivalent to adding an extra 1.5–2.7 min of sun exposure of UVA and 17–26 s of UVB per day, depending on the type of UV nail lamp used [24].

Ultraviolet gels are preblended and not mixed with another substance to initiate the polymerization (curing) process. Until recently, UV gels were blends of urethane acrylate oligomers with photoinitiators (1–4%), crosslinking monomers (~75–95%), and catalysts, e.g. dimethyltolylamine (0.7–1.2%). More recent formulations use urethane methacrylate oligomers and monomers to lower the potential for adverse skin reactions. Slow curing rates associated with UV-curing products allow atmospheric oxygen to prevent surface cure, called the
“oxygen inhibition layer,” and contain partially unreacted material. This can also be observed with certain types of liquid monomers, i.e. “odorless” products utilizing hydroxyethyl or hydroxypropyl methacrylate (HEMA or HPMA) as the main reactive monomer. Direct skin contact with the inhibition layer should be avoided [25].

Like their counterpart, two-part liquid and powder artificial nails, UV gel nail enhancements may be clear, slightly tinted, or heavily colored. First, the natural nail is cleaned, lightly filed, and coated with adhesion promoters or base layers, which may be either evaporation or UV cured. The thick UV gel is then applied to the nail plate and finished in a similar fashion to the liquid and powder systems to produce very similar-looking results. A notable difference is that these coatings are then placed under a
UVA lamp for 2–3 min per applied layer because UVA does not penetrate more than a few millimeters into the gel material, so the UV gels are applied and cured in several successive layers. UV gels may also be applied over plastic nail tips or non-stick nail forms to lengthen the appearance of the natural nail, as described previously.

Ultraviolet gel artificial nails designed to be removed more easily are called “soak-off gels.” These products do not remove any faster than traditional liquid and powder products, typically 30 min soaking in an acetone-based product remover, but are more easily removed than traditional UV gel nails, which can only be removed by carefully filing with an abrasive. This type of artificial nail coating is less durable and must be removed and replaced every 6–8 weeks.

Colored UV gels have long been available but are not such a successful replacement as a permanent nail polish. However, more recent developments of easily applied and removed UV-curing nail polish have replaced this application.

**Cure versus proper cure and allergic potential**

Artificial nails are based on polymerization of monomers and oligomers by polymerization initiators. These formulations contain specific polymerization initiators that utilize heat or UV energy to drive the reactions to completion. They do not cure via visible light. If the formulas contain an improper amount of initiator or are not exposed to the correct type of energy in the proper intensities, this can lead to improper cure. Excessive amounts of initiator or energy can lead to overcuring, while the converse can lead to undercuring. Overcure can produce excessive heat that may result in thermal burns to the nail bed, onycholysis, and subsequent infections of the exposed nail bed. Undercuring is more problematic, because it is not easily recognized and therefore not quickly resolved. Excessive amounts of unreacted monomers/oligomers may become trapped inside the polymer matrix, and can be released later when the nail coatings are filed/abraded, or they can be extracted into the solvent during removal, so skin exposure to uncured material becomes unavoidable unless these coatings are properly cured to a high degree, e.g. >90%. Excessive exposure to improperly cured dusts/filings can lead to adverse skin reactions.

For the two-part monomer/polymer nail systems, the initiator is in the powdered component. Using too little powder and therefore too little thermal initiator is a common reason for undercured nail coatings. This can also occur when a powder is used that was not designed for use with this particular monomer liquid, because various powder formulations contain varying amounts...
of the thermal initiator, benzoyl peroxide. The concentration of initiator in the powder is predetermined by the manufacturer to match the reactivity of the monomer liquid component. When used in the correct ratio of monomer (liquid) to polymer (powder), this will help to ensure a high degree of cure is achieved, e.g. >90% with 10 min. In salons, the tendency is to use too much monomer liquid which can result in dusts or filings that contain excessive amounts of unreacted monomer, and if excessive skin exposure occurs can lead to adverse skin reactions.

UV-curing systems are one-component gel-like materials which contain photoinitiators activated by UV energy, primarily between 400 and 340 nm. Some UV lamps have broad band emissions that peak at 405 nm, but the photoinitiators used primarily absorb/utilize the wavelengths below 400 nm, so these formulations are all UV curing. The degree of cure is therefore determined by wavelengths, intensity, exposure time, and thickness of the applied coating. Nail technicians often mistakenly use the incorrect nail lamp unit because they do not realize these units must be properly matched to the chemistry of the UV gel to ensure a high degree of curing without creating excessive heat. Even the distance from the fingers to the UV source is critical to ensure a high degree of cure. There is no possibility of developing a so-called “universal nail lamp,” even though some irresponsible manufacturers deceptively market their nail lamp units in this fashion.

Latest innovations in nail coatings

Ultraviolet light-emitting diode technology

The higher UV intensity obtainable by using light-emitting diode (LED) technology has been utilized to more rapidly and thoroughly cure UV gels. These nail lamps are more efficient because their output is focused in a narrower range, and thus they emit more of the nearly visible portion of the UVA spectrum needed by some photoinitiators to drive polymerization reactions to completion. Many users are confused by the marketing of these nail lamps which sometimes erroneously infers that “LED” is a type of energy that is unrelated to UV and yet still polymerizes the coatings. Even some medical professionals do not appear to understand this technology, since some advise their clients to cure via LED and forego using UV nail lamps, which clearly does not make scientific sense.

One of the holy grails of nail polish coating is one that can last for at least 2 weeks without any signs of chipping, peeling, or cracking. Typically, nail polish can be expected to last no more than 3–4 days before it begins to break down and/or lose adhesion. This is due to the inherent brittleness of the nitrocellulose film former, which is often blended with softer resins, e.g. tosylamide/formaldehyde resin, polyvinyl butyral, or polyester resins. Plasticizers can help flexibilize these resins. Camphor and dibutyl phthalate (DBP) have long been used for this purpose; even so, the European Union banned DBP in 2004, despite authoritative findings regarding DBP’s safety in nail polish [26]. DBP has since been replaced by other plasticizing agents such as triphenyl phosphate, trimethyl pentanyldisobutylate, acetyl tributyl citrate, and sucrose benzoate. Even so, none of these are able to prolong the length of time nail polish can be worn without breakdown. Not only is this inconvenient for those who wear nail polish, but the US Centers for Disease Control (CDC) have identified this as a potential risk in a hospital setting and have documented that subungual areas of the hand harbor high concentrations of bacteria, most frequently staphylococci, gram-negative rods, e.g. *Pseudomonas* spp., Corynebacteria, and yeasts [27–29]. Freshly applied nail polish does not increase the number of bacteria recovered from periungual skin, but chipped nail polish may support the growth of larger numbers of organisms on fingernails [30, 31].

The recent development of nail salon-applied UVA-curing nail polish can provide a viable solution to these issues. These new UVA-curing nail polishes (also known as UV gel manicure) are solvent based and are applied in the same fashion as traditional nail polish, but with an important difference. They have far superior adhesion, durability, and crack resistance, therefore they are much less likely to harbor pathogens than traditional nail polish. They contain multifunctional (meth)acrylate monomers, oligomers, and UV-sensitive photoinitiators which trigger polymerization to harden the coating when exposed for several minutes to the same relatively low-intensity UVA nail lamps used in salons. The result is a cross-linked coating that wears up to 3 weeks without developing any visible defects, after which it is easily removed with a wooden stick in 5–15 min, depending on the coating’s formulation and cure, after applying a cotton pad soaked with acetone over the coating. These products cannot be used to create an artificial nail and therefore do not extend the plate and so cannot increase the surface area under the nail plate, which the CDC has identified as another risk factor that can increase the numbers of bacteria found on the hand. Also, because this new type of colored nail coating remains chip and crack free, these colored coated nails are much less likely to harbor and/or transmit microorganisms, making them preferable in a hospital setting.

“Press-on” nail art coatings

Self-adherent colored plastic films are affixed to the nail plate to provide a nail polish-like color (Fig. 19.18) with even highly intricate and beautifully artistic designs.
The cosmetic benefit is achieved quite quickly and easily. These newer-type films wear moderately well on fingernails and have superior toenail adhesion. The coatings are applied and removed by heating with a blow dryer to soften the film for easy removal and can be worn for several weeks. When properly removed, there is minimal nail plate surface stripping.

### Electric abrasive files

Motorized electric files are used to rapidly reduce the thickness of artificial nails. Different abrasive bits are used and some create more friction than others (e.g. diamond bits), therefore they can potentially create more heat that may damage the sensitive nail bed tissues, leading to onycholysis. Carbide bits shave layers, rather than grind, and therefore produce less heat and dust. Most abrasive bits can and must be properly cleaned and disinfected between clients. However, paper sanding bands designed to fit over a supporting mandrel are considered single-use only items and must be properly disposed of between clients.

Much of the damage associated with artificial nail products is actually a result of incorrect, overly aggressive use of electric files. Improper use can lead to serious damage to the nail plate, bed, eponychium, hyponychium, and lateral side walls. These devices should not be used on the natural nail and must be used judiciously by nail technicians when shaping the artificial nail.

### Temporary/press-on artificial nails

Preformed, plastic prosthetic full nails may be used as temporary artificial nails, but are usually not worn for more than 48 h and are stuck into place with CA adhesives which may have accompanying hazards [32, 33]. The cosmetic effect is fair, but not nearly as natural looking as the artificial nails described above.

### Medical issues related to artificial nail coatings

- **Nail biting and hang nail picking:** may be discouraged by a regimen of nail care, particularly through the use of color or nail art to help patients to protect their nails from injury.
- **Paronychia:** occasionally appears when poor manicuring skill causes skin penetration by sharp and pointed implements or misuse of electric files and from incorrect cleaning and disinfection of implements [34] (Fig. 19.20).
- **Ridging:** transverse ridging of nail plates, as well as transverse leukonychia, may result from overzealous use of manicure tools in the vicinity of the lunula, particularly in association with the improper use of high pH cuticle removers and sharp metal pushers. These are actually grooves in the nail plate caused by disruptions in growth.
- **Nail discoloration:** deeper shades of red and brown nail enamel may cause mild staining of the nail plate, depending on the porosity of the nail’s surface [35] (Fig. 19.21). This is often caused by leaching of dyes from nail polish (e.g. D&C Red nos 6, 7, and 34; FD&C Yellow N° 5 Lake) into the upper surface of the nail plate where it concentrates over time. Using a base coat under the nail polish can both improve adhesion and reduce surface staining.
Surface white spots/patches: most often caused by improper, overly forceful removal of nail coatings via prying and/or scraping of the plate's surface with wooden, plastic, or metal implements. Nail coatings, including nail polish, should never be forcibly pried, peeled, or picked from the nail plate or surface damage becomes much more likely (Fig. 19.22). Magnification of these areas of damage demonstrates that the white spots are caused by mechanical disruption of nail plate surfaces [36].

Onycholysis: often a result of overly aggressive treatment during the manicure (Fig. 19.23a–c), or prior to application of artificial nails, e.g. improper use of abrasive files resulting in separation of the plate from the nail bed. It may also result from excessively elongating the distal portion of the nail plate with an artificial nail and thereby increasing the potential of an accident resulting in this type of physical trauma [25]. Although nail polishes have been mentioned in association with onycholysis, considering their extensive use worldwide, the cause-and-effect relationship must be considered as most unusual.

Overly aggressive use of pointed metal or wooden instruments may cause injury to the hyponychium, breaking this seal and leading to weakening of the interface between the nail bed and nail plate leading to onycholysis. Heat generated by friction from heavy-handed use of abrasive files is also a cause of onycholysis.

Pseudopsoriatic nails: describes clinical patterns that include onycholysis and severe subungual hyperkeratosis [37, 38]. Surface discoloration and improper removal loosen the upper layers of the nail plate and cause localized pitting and peeling/delamination. Patch testing to methacrylate is positive. However, thinning of the nail is produced by overfilling with an abrasive; this represents a leading cause of nail damage. Prying, scraping, or other types of forceful removal constitute the second leading cause.
of surface damage. An association of pincer nail deformity, yellowish chromonychia, and numerous nail pittings have been induced by gel polish [39].

- **Pterygium formation**: many salon workers do not realize they are the cause of their client’s poor skin condition around the nail. Cutting the eponychium tissue or other injuries can lead to abnormal skin growth (dorsal pterygium). When the eponychium is severely damaged, the proximal nail fold may not release from the nail plate and can be stretched to extend a considerable distance onto the nail plate. This stretching creates a thinner layer of skin that is too often cut away when it is mistaken as an “overgrowth of cuticle” but actually is pterygium that should not be cut since this can worsen the condition and may lead to infections. Recently, some cases of pterygium inversum unguis secondary to nail polish have been reported. Most patients have experienced resolution of this condition upon discontinuation of gel polish use [38].

**Allergic contact dermatitis**

Conventional nail care and nail polish products are rarely associated with local (fingertip) allergic eczematous-type contact reactions [37]. Patchy eruption on distant sites, such as eyelids (Fig. 19.24), neck, and deltoid areas, even the genitals, may be related to contact with fingernails coated with nail polish. Besides ectopic dermatitis, allergic airborne contact dermatitis should be suspected when the lesions involving the face, neck, and ears are

*Figure 19.23* Onycholysis due to cosmetic procedures at different stages (sculptured onycholysis). (a,b) Nail plate–nail bed separation. (c) Nail plate–nail bed and distal matrix separation.

*Figure 19.24* (a) Sites of origin and transfer of allergens. (b) Contact dermatitis of the eyelids. Courtesy of C. Bonu.
symmetrical. The allergen in nail enamels is usually the thermoplastic resin.

Diagnostic patch testing with nail polish should be performed without occlusive covering and with dry nail polish films to avoid false-positive reactions from solvent. Interestingly, ectopic contact dermatitis from henna used to dye nails has been reported [40, 41].

Tosylamide/formaldehyde resin has been related to desquamative gingivitis [42]. In the case of nail enamel base resins, several different types are used, so switching brands may be a reasonable approach.

Recommending that the patient uses nail polish labeled “hypoallergenic” provides no guarantee and is dermatologically without merit. Such claims mislead practitioners and confuse patients.

Overall risk

Precise figures are not available for the number of adverse reactions related to the use of cosmetics in general, and certainly none for nail care products in particular. However, by reviewing data collected from several sources, a reasonable estimate can be made.

In a 64‐month interval between 1977 and 1983, 12 dermatologists representing various geographical areas of the USA studied 713 patients with cosmetic dermatitis. Of this number, 55, or 8%, had adverse reactions to the entire category of nail preparation [43].

Conclusion

No matter how one reviews and analyzes the figures from all sources, the incidence of untoward reactions related to the use of cosmetics by the general population is very small (approximately 2 per million units sold). Nail care products as a subgroup probably account for less than 10% of cosmetic reactions. Rarely are there injuries of any significance due to acrylate or methacrylate monomers/oligomers used in application or removal of artificial fingernails, even though they are widely used around the world. Many reported problems probably relate to the lack of information, training, or skill required to properly apply and remove artificial nails, which can further raise the potential for injury. One of us, Schoon, presently offers on-line generic video education for nail salon workers in order to address the lack of fact-based technical information, especially where working safely is concerned (www.FacetoFacewithDougSchoon.com).

Nail care products are fashion orientated and we have not reviewed all the different products or services available, because they would lack pertinence. There are many products, implements, and devices for maintaining clean, well-groomed nails to satisfy individual needs, providing substantial benefits with small risk. The physician can and should be well versed in the nail care and adornment that aid patients to achieve an improved positive self-image.

References

Cosmetics: the Care and Adornment of the Nail

Chapter 20

Trauma from Footwear and Pedal Deformities

Bertrand Richert

Department of Dermatology, Brugmann, St Pierre and Queen Fabiola University Hospitals, Université Libre de Bruxelles, Belgium

Introduction

In routine nail consultations nail dystrophies from footwear and pedal deformities equal or even exceed the number of cases of onychomycosis. It may be difficult for the practitioner to imagine the number of nail lesions induced by footwear and foot deformity, especially because the dermatological literature is extremely sparse on the topic of podiatry. Dermatologists typically see the nail apparatus in static terms and frequently give little consideration to the functional aspects of the digit. This is particularly relevant for the toenails, for which it is diagnostically and therapeutically mandatory to consider the toe and the foot as a whole. Their repetitive movements may cause nail disease or aggravate and perpetuate diseases of the nail due to some other primary cause [1, 2].

It is striking that feet of equal size but of different shape must adapt to the same shoe. Empiric standards of shoe size that were determined more than a century ago (1886) are still applied today [3, 4]. A very wide study demonstrated that no pair of feet had identical feet: in three-quarters of cases there is a difference of about half a size between the two feet, and in the remaining quarter, one size or more. Sixty per cent of individuals have a 0.5 cm width difference between their two feet [5].

Podiatry literature commonly describes three foot shapes based on the length of the great toe: the Egyptian foot, the most frequent (60%), with a prominent great toe; the square foot, that has a second toe as long as the first one (25%); and the Greek foot, with a second toe longer than the first one (15%) [6]. All these variations naturally intervene in foot–shoe incompatibility.

Being an appendage to the foot, the nail is often contained in footwear for long periods of time and is exposed to the forces generated during gait. The vast majority of footwear-induced nail dystrophies are observed in the elderly [7] and result from toenail–shoe conflicts over a lifetime [8, 9]. They may occur earlier if ill-fitting footwear is worn [10, 11]. When considering toenail problems, it is of great importance to take an overall view of the whole foot: common problems often arise as a result of its dynamic function.

Detective work is often needed to highlight causative factors [12–14]. This includes analysis of:

- constraints from footwear
- foot shape and added orthopedic deformities
- occupation and other factors.

Foot function

The human foot has evolved to carry out a specific function and to assist smooth and efficient locomotion. In undertaking this task, the foot has developed the ability to alter its structure and its function within a single footstep. To understand this, one should understand the normal gait cycle (Fig. 20.1). During normal walking, the
first stage (heel strike) begins when the heel meets the ground. To permit shock absorption, the foot must become a flexible unit. It does this by pronation: eversion of the calcaneum, lowering of the arch, and slight elongation in the foot length. Subtalar joint pronation unlocks the midtarsal joint so that effectively the foot flexes to accommodate to the ground at heel strike. This pronation continues until the whole of the foot is flat to the floor (midstance or full foot). For this foot to take full body weight as the opposite foot leaves the ground, it must now become a rigid unit. Once the other limb has passed the plantigrade foot and undergoes heel strike, the foot begins propulsion as the heel lifts, so that body weight is shifted onto the forefoot and the toes. To stabilize the foot and propel the body forward, the foot becomes supinated (a movement involving the subtalar and midtarsal joints whereby the calcaneum inverts, the arch is raised, and the foot is shortened). This movement effectively locks the foot into rigidity, allowing a stable platform for propulsion.
Constraints from footwear

Although shoes have been worn for thousands of years for the main purpose of protecting the feet from the environment, recent studies have implicated shoes as the principal cause of forefoot disorders seen in females [15]. Incorrectly fitting footwear is common in older people and is strongly associated with forefoot pathology and foot pain. It has been demonstrated that, even in the elderly, women wore shoes that were shorter, narrower, and had a reduced total area compared to their feet than men [16].

The ideal shoe should have:

- **Suitable fastening**: a foot in a shoe without an adequate fastening suffers as it moves freely in the shoe and slips forward into the toe box region, traumatizing the distal aspect. Laces are, by far, the best method of fastening a shoe and the higher the laces come up the front of the shoe, the more restraint and support are given to the foot. For patients who cannot tie laces, due to arthritic fingers or spine, Velcro straps make a reasonable substitute.

- **Adequate room within the shoe** to restrict rubbing and other trauma to the forefoot and nails. Adequate depth and width ensure that there is no excess pressure on the digital areas; together with a suitable fastening, this ensures that the foot stays well back from the tip of the shoe and into the heel. Manufacturers still produce types of shoes with inadequate width and depth in the toe box area. One can often see the effects of this when toe outlines are visible from the outside of the shoe. When looking at toenail problems, it is wise to feel inside the upper of the shoe; one may feel a dent or tear in the inner lining of the shoe corresponding to the affected digit. Other clues can be given by the nail itself. A nail with unusual pigmentation may have acquired this from rubbing on the leather of new shoes. More commonly, though, a single toenail with a very “polished” sheen to it can be the result of continuous rubbing on the soft lining of an upper of a shoe.

- **A heel height no greater than 30–35 mm**. If heels are too high, the foot is forced forward into the toe box with every step, traumatizing the anterior part of the foot, especially around the nail apparatus and apices. The higher the heel, the more damage is likely to occur.

In order to understand the pathogenesis of footwear-induced nail dystrophies, one has to be aware of the different types of constraints applied by the shoe on the toenail unit.

**Lateral constraints**

These result from the pressure of the shoe on the hallux and fifth toe and the pressure from adjacent toes. These are secondary to trying to fit a rectangular shape, the foot, into a triangular shape, the shoebox [10].

**Anteroposterior constraints**

These arise from repeated buffeting of the toes, secondary to the foot moving forwards and backwards during gait. This mostly affects the great toe but sometimes the second one, as observed in the Greek foot (Morton’s toe) [11]. The other toes are less affected, unless there is an orthopedic dystrophy. These constraints are enhanced by high heels: the body weight is transmitted to the forefoot that slides forward, promoting hammer toes [17, 18] with secondary nail dystrophies.

**Superoinferior constraints**

Superoinferior constraints also exist. They arise from the tip of a shoe that is not deep enough. These shoes are typically women’s shoes. This induces friction between the thickest toe, the great toe, and the roof of the shoe [19].

**Resulting clinical features**

The nail has a limited repertoire of clinical responses resulting from these constraints. They consist mainly of thickening of the nail plate itself (onychauxis or pachyonychia), the nail bed (subungual hyperkeratosis), or both structures simultaneously, or detachment of the plate from the bed (onycholysis). Leukonychia and longitudinal melanonychia may also appear.

**Lateral constraints**

Friction of the shoe against the medial part of the great toenail leads to a hyperkeratosis of the distal part of the lateral fold called onychophosis (Fig. 20.2). The same condition may be observed on the lateral part of the fifth toe. Pressure of adjacent toes may induce hyperkeratosis of both lateral nail folds [20] (Fig. 20.3).

Figure 20.2 Onychophosis on the medial side of the great toenail.
Rubbing of the proximal nail fold against the shoe may activate the matrical melanocytes inducing a frictional melanonychia [21] that is commonly observed on the lateral aspect of the fifth toenail (Fig. 20.4). It is often associated with thickening of the plate. In some instances, it may be observed on the fourth and even third toe (Fig. 20.5).

Tight, pointed shoes enhance the lateral deviation of the great toenail, forcing the second toe to override the lateral aspect of the great toenail with subsequent frictional onycholysis [22] (Fig. 20.6a–c). This onycholysis develops in an area where the adherence of the plate to the bed is already weak [23]. The same mechanism is responsible for subungual hematomas, almost always triangular in shape. The major factor that encourages hematomas at that spot is the lack of cushioning subcutaneous fat deep to the nail bed [24]. Hematomas are common and frequent in patients being treated with aspirin or warfarin [24–26] (Fig. 20.7).

Permanent pressure from the second toe on the lateral part of the great toenail, which may result in a soft tissue depression, may account in some part for the occurrence of ingrowing toenail, especially pincer nails (Fig. 20.8a,b) [27, 28]. Pressure from the shoe and/or from the adjacent toe may in some instances be responsible for a hypertrophic nail fold, called hypertrophic lip (Fig. 20.9). This deformity promotes onychocryptosis [29].

Seams running over the distal part of the shoe may rub on the proximal nail fold and induce chronic paronychia with possible acute flare-ups.
Anteroposterior constraints

During gait, the foot moves back and forth in the shoe. When the great toenail is long, repeated buffeting against the tip of the shoe may induce distolateral nail fractures. The same mechanism may lead to transverse leukonychias [30] (Fig. 20.10), which may in some rare instances be observed on the toes. The white bands are more pronounced on the side where the nail is longest, accounting for more intense buffeting.

_Lamellar splitting_ of the distal edge as well as Beau’s lines (Fig. 20.11) are commonly observed in sportsmen whose feet are subjected to frequent starts and stops as in tennis, soccer, basketball, and squash.

Superoinferior constraints

_Onychoclavus_ (or heloma) is a horny plug that develops in the median part of the distal bed. It occurs in the
thickest part of the great toe, where friction is maximal. It generates a lot of pain from the pressure between the bone and the plate. It induces a circumscribed onycholysis that can be easily clipped away, allowing its exposure (Fig. 20.12a–c). Removal may be undertaken by gentle curettage but in some instances the lesion is very deep and needs excision under local anesthesia. Friction may also provoke intralosomal hemorrhages (especially in patients taking aspirin or warfarin) and the lesion may appear as a dark painful spot in the distal nail (Fig. 20.12c).

Friction against the upper part of the shoe may also induce onycholysis [31]. This phenomenon is observed mostly in women whose shoes are not deep enough at their distal tip; friction occurs on the thickest toe, i.e. the great toe. Onycholysis was also reported in the 1970s with platform shoes: the rigidity of the soles impaired the natural dorsiflexion of the toes, the foot being thus limited to a back and forth motion within the shoe. Friction on the upper part of the shoe generated onycholysis on several nails, especially the great toenail [32]. The reappearance of platform shoes in recent years has not produced similar side-effects. In contrast to their ancestors, new shoes have supple and flexible soles, limiting the friction of the toenails against the roof of the shoe.

Foot shape and added orthopedic deformities

Chronic trauma to the nail unit may also result from superimposed faulty biomechanics [14, 33]. Most orthopedic abnormalities are acquired and precipitated by long-standing use of ill-fitting footwear (especially high heels) [34, 35] and/or underlying osteoarthritis, which accounts for their occurrence in the elderly. Some of them may be congenital, such as Morton’s toe.

Accidental trauma and surgery may also be an etiology. Occupational factors should be taken into account: the amount of time a patient spends wearing particular shoes may affect the severity of nail problems. Thus, an orthopedic abnormality will more rapidly affect the nail unit in a sportsman [36] than in a sedentary individual. Occupational footwear, such as steel-capped shoes, may also be a precipitating factor.

Morton’s toe (also called Greek foot, in reference to Greek statues) is characterized by a second toe longer than the first one, but the real problem is in fact the shorter great toe. In some cases, the great toenail appears
shorter due to early closure of the epiphyseal line. To adapt to the length of the shoe (which is invariably calculated according to the size of the great toe), the second toe is forced into plantar flexion. The amplitude of this downward flexion is proportional to the length of the toe: the longer the toe, the greater the flexion. With time, several nail alterations may develop. Pseudoclubbing (Fig. 20.13) may be observed. A slight flexion leads to hyperkeratosis of the hyponychium. Severe flexion will promote friction of the whole distal phalanx against the tip of the shoe. This may induce nail hyperkeratosis (Fig. 20.14a,b) and frictional longitudinal melanonychia (Fig. 20.15a,b). In this case, a callosity is often facing the pigmented band. Subungual hematomas due to repeated stubbing are common.

Hammer toes result from a muscular imbalance between the extensor and flexor muscle groups. As in Morton’s toe, deformities will depend upon the severity of the flexion: hyperkeratosis of the hyponychium (Fig. 20.16a,b), onychauxis, frictional onycholysis, frictional melanonychia, subungual hemorrhages.

Hallux valgus (Fig. 20.17a–c) is characterized by an enlargement of the metatarsal head and a general stiffening of the joint; over time, this leads to a fixed dorsiflexed distal phalanx. The nail often protrudes dorsally and is exposed to rubbing and stubbing against the shoe, resulting in onychauxis or onychogryphosis, often associated with hyperkeratosis of the medial fold. The gradual lateral deviation of the great toe forces the second one to override the first one. Progressively, the lateral fold becomes hyperkeratotic from repeated friction, resulting in an onychophosis or a hypertrophic lip. Pressure from the second toe on the lateral portion of the great toenail may promote or aggravate pincer nail. Overlapping of the second toe on the first one may lead to frictional onycholysis of the distal and lateral parts of the great toenail. Subungual hematomas from overriding are common and almost always triangular in shape.

Hallux erectus is due to exaggerated tension of the extensors with laxity of the flexors. This diagnosis is often missed because dermatologists examine the nail apparatus from above. Side examination reveals that the distal nail protrudes dorsally, exposing it to rubbing and stubbing against the roof of the shoe (Fig. 20.18a–d). This very commonly induces a median distal onycholysis or a subungual hyperkeratosis with progressive shortening of the nail bed [37]. Most often the patient complains that the nail is not growing anymore and that he/she never needs to trim it. The nail is in fact being worn down against the upper part of the shoe.

Lateral rotation of the fifth toe is precipitated by osteoarthritis and footwear. The toe is orientated in such a way that the patient ambulates on the lateral part of the nail [27]. The frictional forces occurring between the shoe and the nail will induce hyperkeratotic reactions such as onychophosis. A deep horn plug may develop within the lateral sulcus (Fig. 20.19) and is often accompanied by a facing callosity on the distal interphalangeal joint. It may become extremely painful and
require surgical removal. Peroperative examination reveals that its deepest aspect reaches the bony phalanx. Subungual hematomas are very common in this location, but should be distinguished from frictional melanonychia. For this, dermoscopy is of great help.

Amputation of the great toe will modify the distribution of the forces in the foot. Normally the whole body weight is located on the head of the second metatarsus and spread out on the five toes. After amputation, the force of the great toe is transferred on to the second one, increasing the interactions between the shoe and the tip of the toe, as the second toe is now the longest one. A hyperkeratotic reaction will develop, especially onychauxis. Amputation of a lesser toe usually does not cause any problems as the other toes have more space to spread out in the shoe.

Some authors gathered all these dystrophies under the acronym AGNUS (asymmetric gait nail unit signs) that includes onycholysis, nail bed keratosis, nail plate surface abnormalities, and an abnormal nail plate shape. All these nail dystrophies are associated with skeletal abnormalities and result from an asymmetric walking gait [38]. The same authors showed that AGNUS toenails are predisposed to colonization by non-dermatophyte opportunistic fungi but not dermatophyte fungi [39].
Figure 20.16  (a) Hyperkeratosis of the hyponychium on a Morton's toe. (b) Hyperkeratosis of all lesser toenails (hammer toes).

Figure 20.17  (a) Hallux valgus. Note the pincer nail, the subungual hyperkeratosis, and the Morton's toe with a callosity. (b) Severe hallux valgus with the second toe overlapping the great toenail.
Management

Treatment of footwear-induced nail dystrophies should involve several specialists. The dermatologist will first rule out any other cause, especially onychomycosis. The foot should be examined both in a static and dynamic way (gait). A podiatric consultation with podoscopy will complete the examination and confirm or make more precise the diagnosis of the forefoot dystrophy. Other changes should evoke complementary work-up: neurological disturbances in the lower limb because of diabetes, paresis, or other disorders can lead to changes in muscular tone within the leg. Spasticity or atrophy may lead to imbalances between dorsiflexors or plantarflexors.

Figure 20.18 (a) Hallux erectus. Note the hammer toes and the onycholysis of the distal great toenail. (b) Severe hammer toe and contamination of the onycholysis of the great toenail with *Pseudomonas*. (c) Severe erectus with constant friction against the roof of the shoe leading to subungual hyperkeratosis. (d) Various type of erectus: upper and side views.

Figure 20.19 Painful keratotic plug in the lateral sulcus of the fifth toe.
of the foot which, in turn, result in digital deformities and nail distortion; the latter will vary in relation to the specific paralysis or orthopedic change.

Prescription of insoles is almost the rule and should be done by a skilled podiatrist. Adequate devices will correct hallux erectus and redistribute weight away from the first metatarsal joint. A toe crest will flatten hammer toes, if still reducible. Treatment should remain as conservative as possible in elderly patients who are often receiving multiple systemic treatment and for whom orthopedic surgery should remain the exception. Chemical cautery might be proposed for pincer nails. Diabetes and vascular impairment are not contraindications. One should consider not leaving the tourniquet longer than the 4 min necessary for the cautery.

Overriding phenomena should be corrected with silicon orthoses (Fig. 20.20a–c). These devices lessen or remove friction and relieve patients instantaneously. If improperly shaped, they will hurt the foot and impair walking, and the patient will abandon them. Therefore, off-the-shelf ones are not indicated as their standard shape will not fit every foot. Only customized ones will work and even those may need some slight adjustments to be perfect. Once adapted, they should not be noticed by the patient.

A hyperkeratotic nail can be reduced in size with an electric burr. However, this procedure might be uncomfortable as it generates some heat. Devices with water propulsion do not have this side-effect. Some podiatrists and pedicurists are not keen on using these burrs in patients with impaired vascularization. An alternative is chemical avulsion with 40% urea. After the peripheral soft tissues have been protected with an adhesive zinc oxide plaster, the plate is covered with a thin layer of urea paste, wrapped in an occlusive plastic dressing, and left for 5–8 days. This softens the nail plate and leaves it much easier to trim. This procedure may be repeated as often as necessary to reduce the nail to a thickness at which it fits in the shoe without pain.

Of course, this should be completed with shoes of adequate width and depth. Some brands offer very comfortable shoes, especially adapted for patients with these problems.

References

Part IX
Nail Tumors and Surgery

Chapter 21
Tumors of the Nail Apparatus and Adjacent Tissues

Marcel Pasch1, Eckart Haneke2, Robert Baran3, Luc Thomas4, and Bertrand Richert5

1 Department of Dermatology, Radboud University Medical Center, Nijmegen, The Netherlands
2 Department of Dermatology, University of Bern, Bern, Switzerland; Centro de Dermatologia Epidemis, Porto, Portugal; Department of Dermatology, University of Gent, Ghent, Belgium
3 Hon. Pr. of the University of Franche-Comté; Nail Disease Center, Cannes, France
4 Department of Dermatology, Centre Hospitalier Lyon Sud; Lyon Cancer Research Center (Pr Puisieux); Lyon 1 Claude Bernard University, Lyon, France
5 Department of Dermatology, Brugmann, St Pierre and Queen Fabiola University Hospitals, Université Libre de Bruxelles, Belgium

CHAPTER MENU

| Introduction, 675 | Benign vascular tumors, 722 | Sarcomas, 756 |
| Epithelial tumors, 675 | Malignant vascular tumors, 737 | Pseudotumors, 759 |
| Benign tumors, 675 | Neuroendocrine tumor, 738 | Histiocytic, lymphomatous, and metastatic processes, 767 |
| Premalignant lesions, 700 | Tumors of peripheral nerves, 738 | Histiocytic processes, 767 |
| Malignant epithelial tumors, 701 | Osteocartilaginous tumors, 743 | Lymphoma, 768 |
| Soft tissue tumors, 710 | Benign osteocartilaginous tumors, 743 | Metastases, 768 |
| Benign fibrous tumors, 710 | Malignant osteocartilaginous tumors, 752 | Melanocytic lesions, 770 |
| Malignant fibrous tumors, 721 | Synovial tumors, 752 | |
| Vascular tumors, 722 | Lipomatous and myxomatous tumors, 754 | |

Introduction

In the original sense of the term, a tumor is a circumscribed swelling which may be due to an increase in cells, acellular tissue components, or both. This term therefore comprises many more lesions than just true neoplasms; however, since the nature of a tumor often requires a histopathological examination and the differentiation between pseudotumors, degenerative and reactive tumors, and “true” neoplasms is often somewhat arbitrary, we will deal in this chapter with most lesions clinically appearing as a “tumor.”

Inadvertent, often minor, trauma causes the first symptoms, so that the diagnosis may be further delayed, and many neoplasms may cause bulbous enlargement of the fingertips with nail clubbing due to bone splaying associated with pressure beneath the nail bed [1]. A history of trauma, associated infection, concealment beneath the nail, modifications of tumor behavior produced by the specialized nail anatomy, and variations in pigmentation are all factors that may mislead the diagnostician [2, 3].

Epithelial tumors

Benign tumors

Warts

Etiology

Periungual and subungual warts are caused by many different genotypes of human papillomavirus (HPV). HPV 1, 2, 4, 27, and 57 are generally the cause of benign ungual warts [4]. HPV 16, 18, 52, 58, and 73 are rare causes but are associated with malignant transformation to squamous cell carcinoma [4–6]. Warts are caused by infection of the abraded or macerated skin with HPV [7]. Biting, picking, and tearing of the nail and nail walls are common habits in subjects with periungual warts (Fig. 21.1a,b). This type of trauma is probably responsible for the spread of the warts and their resistance to treatment. Nail biting and picking may also result in spreading of the condition to the face and lips [8]. Since the virus is very resistant to heat, desiccation, and detergents, warts can also be acquired by indirect contact, and not only by direct contact in a susceptible host.
Clinical features
A few weeks to more than 1 year after inoculation, clinical warts will develop as 1 mm to 10 cm nodular or linear fibroepithelial tumors with a rough keratotic surface. Fingernails are involved more often than toenails, possibly because of more frequent exposure of the hands to sources of HPV. Most frequently, they are located on the lateral aspect of the proximal nail fold. Subungual warts initially affect the hyponychium, growing slowly toward the nail bed and finally elevating the nail plate (Fig. 21.2). The nail bed is not often affected although surface ridging may occur; loss of the nail is exceptional. Not infrequently warts of the proximal nail fold produce periungual hyperkeratosis simulating a hyperkeratotic cuticle. A common wart will never invade the nail matrix [9]. Usually periungual warts are asymptomatic though fissuring may cause pain. Tender periungual nodules are infrequent [10]. Longitudinal grooving is rare (Fig. 21.3). Exceptionally, a wart may develop underneath the proximal nail fold that appears swollen (Fig. 21.4a). Surgical elevation of the proximal fold exposes the lesion [11] (Fig. 21.4b). Multiple warts distorting the nail unit are commonly seen in immunosuppressed patients (Fig. 21.5a, b). Global nail dystrophy of all 20 nails was a very unusual presentation of HPV infection (type 57) of the nail bed and the matrix in an otherwise immunocompetent patient [9].

Differential diagnosis
The main differential diagnosis remains Bowen disease: any persistent and recalcitrant peri- or subungual wart as well as any recently appeared verrucous lesion of the nail unit in men above the age of 40 years should raise the suspicion of squamous carcinoma in situ and should be biopsied [6].

Figure 21.1 (a,b) Multiple periungual warts are common in nail biters/pickers.

Figure 21.2 Subungual wart lifting up the nail plate.

Figure 21.3 Wart on the proximal nail fold: pressure has caused a depression on the nail plate.
Differential diagnosis includes onychophosis affecting a lateral fold of the toenails, subungual filamentous tumor, subungual vegetations of amyloidosis, subungual corn (heloma), verrucous epidermal nevus, inflammatory linear verrucous epidermal nevus (ILVEN), and multicentric reticulohistiocytosis. Subungual warts are painful and may mimic a glomus tumor. Bone erosion from verruca vulgaris might have been observed [12–16]. However, some of these cases may have been keratoacanthomas since the latter, as well as squamous cell carcinoma and verruca vulgaris, are sometimes indistinguishable by clinical signs or on a partial biopsy alone.

**Pathology**

The histopathology of subungual and periungual warts is similar to that of common warts found elsewhere. Cytopathic effects are not as marked as in plantar warts. An inflammatory infiltrate may be present when the wart has been traumatized repeatedly. Histopathology is particularly needed for inconspicuous warts of the hyponychium presenting only as a slightly thickened skin-colored area that swells and, after immersion in water, turns white more rapidly than the surrounding skin. Histopathological examination shows considerable thickening of the epidermis, vacuolization of the granular layer, and a loose basket weave-like horny layer (E. Haneke, unpublished observation).

Tuberculosis cutis verrucosa (butcher’s nodule, prosector’s warts) may occasionally pose difficulties in differential diagnosis, but it is very rare around the nail. Haneke [17] has described a warty growth in the proximolateral nail groove which he termed “onycholemmal horn” (Fig. 21.6a,b); the histology was similar to proliferating trichilemmal cyst. A similar histology was observed in an onycholemmal cyst (E. Grosshans, personal communication).

When mucinous syringometaplasia involves the distal nail bed, its clinical resemblance to warts is striking. Histology revealed a focal invagination of the epidermis lined by squamous epithelium, with one or several
eccrine ducts leading into the invagination. The eccrine duct epithelium contained mucin-laden goblet cells, and there was mucinous syringometaplasia of the underlying eccrine coils [18].

**Management** (Box 21.1)

**General principles**
Warts often disappear spontaneously, especially in healthy children. They have a natural life span of about 4–5 years, but this duration may exceed the patience of the patient or physician [19]. Aggressive measures are not recommended because of spontaneous resolution. Furthermore, treatment of periungual warts is often frustrating. A stronger indication for treatment is warts in immunocompromised patients that are often present for years and have an insidious growth. Warts should be aggressively treated in patients who are planned to be strongly immunosuppressed (e.g. on a waiting list for organ transplant).

**Topical treatments**
A recent review extensively discussed the treatment of ungual warts [4]. Topical therapies may help to control the growth of the warts.

*Keratolytic agents* are effective and mostly contain salicylic acid, sometimes lactic acid, bichloroacetic acid, or trichloroacetic acid.

*Virucidal agents* containing glutaraldehyde or formaldehyde are as effective as keratolytic agents. Cidofovir is an antiviral agent that inhibits the activity of DNA polymerase of various viruses. In a retrospective study using 3% cidofovir cream in 41 patients, complete clearance was noted in 56% of recalcitrant periungual warts [20].

*Caustic agents* may also be used. Samman [21] recommends saturated monochloroacetic acid. It is applied sparingly, allowed to dry, and then covered with 40% salicylic acid plaster cut to the size of the wart and held in place with adhesive tape for 2–3 days. After 1–2 weeks most of the wart can be removed and this procedure has to be repeated. This may sometimes become painful when most of the overlying horny layer has been removed [22]. Subungual warts are treated similarly, after cutting away the overlying part of the nail plate. Hand or foot baths, as hot as tolerable and performed twice daily, are valuable supportive measures. Due to the vasoconstrictive action of nicotine, smoking will delay healing.

*Topical immunotherapy* is a more time-consuming but effective and painless approach for recalcitrant warts. They may respond to squaric acid dibutylester [23] or 2% diphenylcyclopropenone (diphenycrponge) [24], an obligate sensitizer which has replaced 2% dinichlorobenzene that is mutagenic and therefore can no longer be recommended in humans [25, 26]. Purified protein derivative of tuberculin bacilli [27], BCG vaccine [28], and Mycobacterium W vaccine [29] have been used as non-specific stimulants of cell-mediated immunity to achieve resolution of warts.

*Cantharidin* (0.007%) has a long history in the treatment of periungual warts [30]. “Cantharone” is applied to the lesions and covered by a plastic tape for 24 h.

---

**Box 21.1** Treatment ladder for peri- and subungual warts

1) Stop nail picking and biting
2) Any harmless popular trick
3) Keratolytics in the long term
4) Imiquimod (adults)
5) Pulsed-dye laser
6) Bleopuncture

---

**Figure 21.6** (a) Onycholemmal horn. (b) Histology.
The resultant blister roof is removed and the remaining wart retreated at 2-week intervals, three to four times if necessary. Tkach [31] suggested a trick when using cantharidin for warts in order to avoid blister formation, which he believed caused spreading of the wart (a similar complication occurs with liquid nitrogen). After applying cantharidin, the wart is covered with paper tape. The patient is given an alcohol sponge and instructed to wipe off the cantharidin in 2 h. If there is not enough reaction, the cantharidin is left on progressively longer with subsequent visits. For children Cantharon™ is diluted 1 : 1000 with a 1 : 1 mixture of isopropyl alcohol and acetone and may be left longer on the skin.

**Topical imiquimod** 5% cream was used successfully in widespread HPV 42 periungual warts in a patient with AIDS [32], and an open trial in 15 patients with resistant and recurrent periungual and subungual warts showed 80% complete resolution after a mean time of 3 weeks [33]. In order to reduce hyperkeratosis and optimize drug penetration, 50% salicylic acid in white petrolatum was applied topically under an occlusive dressing for 3–5 consecutive days to periungual and exposed portions of subungual warts prior to imiquimod therapy. Application of imiquimod under occlusion but without prior kerolytic treatment has also shown to be effective in a 26-year-old man with extensive and recalcitrant verrucae verrucae of the great toe [34], and in a 14-year-old girl with 10 periungual warts unresponsive to cryotherapy [35].

**5-Fluorouracil** has been used for treating periungual warts, especially under occlusion. Onychodystrophy [36], melanonychia [37], and painful onycholysis may appear [38].

**Tea-tree oil** was reported to be successful with warts on the dorsal side of a distal phalanx and on the fingertip in a pediatric patient [39].

**Intralosional treatments**

**Bleomycin** has been strongly recommended for recalcitrant warts [40]. Using bleopuncture technique [41–43], bleomycin 0.1–1 mg/mL is dropped on the wart and pricked into the lesion by multiple rapid stabs with a needle. With this multiple puncture technique with a bifurcated vaccination needle under local anesthesia to introduce bleomycin sulfate (1 mg/mL sterile saline solution) into warts, Shelley and Shelley [44] obtained elimination of 92% of a random series of 258 warts after a single treatment. AlGhamdi and Khurram [43] used the translesional multipuncture technique with a lower dose of bleomycin (0.1 mg/mL). They reported 87% complete clearance in 15 patients at 6-month follow-up with only one injection. Van der Velden et al. [45] recommended treatment with increasing concentrations of bleomycin using the Van der Velden Derma-injector which is a modified tattooing machine. Transitory [46] and permanent [47–49] nail dystrophy and even complete nail loss following intralosional injections of bleomycin for periungual warts has been reported (Fig. 21.7) and for this reason the authors never use bleomycin in the matrix area and prefer the stabbing or micropuncture method to injections [43]. Vasospastic effects such as permanent Raynaud phenomenon from intralosional therapy may occur even when using a reduced dose [50].

**Physical treatments**

**Photodynamic therapy** using 20% delta-aminolevulinic acid, alone or combined with CO2 laser, has been reported to be effective in ungual warts [51, 52]. This could not be confirmed in a prospective, randomized, double-blind clinical trial [53].

**Cryotherapy** with liquid nitrogen is often the first choice for a small wart. It causes blistering with the blister roof containing the epidermal wart component if the treatment succeeds [54]. However, when treating the proximal nail fold, freezing must not be prolonged since one may easily damage the matrix, which may result in circumscribed leukonychia (Fig. 21.8a) or even nail dystrophy (Fig. 21.8b). Though scarring is rare, permanent onycholysis with pterygium formation has been reported [55]. Cryotherapy of warts on the dorsal aspect of the distal interphalangeal joint was responsible for mallet finger secondary to rupture of the extensor tendon in two children [56]. Particular side-effects of cryosurgery include secondary bacterial infection (rare), Beau’s lines, onychomadesis, nail loss, and pain due to subungual edema, which is often worse in the very young and very old. Pain is limited if the freezing times are carefully controlled, and prophylactic analgesic and subsequent antiinflammatory treatment are provided. Oral aspirin 600 mg three times daily, beginning 2 h before and for 3 days after treatment, is helpful. Pretreatment application of clobetasol propionate [57], beneath an
occlusive tape such as Blenderm, reduces the inflammatory response to the freeze. Massages with this steroid may be continued twice daily for 3 days.

**Cold blade surgery** is contraindicated due to high recurrence rate and resultant deformity. Destruction using curettage and electrosiccation may produce considerable scarring.

**Lasers** have been used, especially the CO₂, pulsed dye, and neodymium-doped yttrium aluminum garnet (Nd:YAG) laser, but in daily practice their efficacy is not always convincing, and permanent nail dystrophy is possible after ablation of periungual warts [58–61] (Fig. 21.9). Long-pulsed 1064-nm Nd:YAG laser induced complete clearance in three patients with recalcitrant periungual and subungual warts [62]. Pulsed-dye laser has also been used successfully for recalcitrant warts with a claimed excellent side-effect profile [63]. Laser therapy is generally recommended as second line for recalcitrant warts but some authors propose pulsed-dye lasers as "first-line therapy" for periungual warts [64].

Many lay and medical people have "tricks" for attempting to cure warts. A suggested treatment is "wrapping" with Micropore, for example, followed 2 weeks later by the careful application of liquefied phenol and then a drop of nitric acid to the lesion. The fuming and spluttering that occur look efficacious and the wart turns brown [65]. This is most probably a suggestive therapy.

**Systemic treatment**

*Cimetidine*, thought to be an immunomodulator, has been disappointing in the treatment of recalcitrant periungual warts [66, 67] despite some positive anecdotal reports [68, 69].

**X-ray and radium treatments** are highly carcinogenic and must no longer be used.

**Follow-up**

Since the incubation period of human warts may be up to several months, consistent follow-up, even after seemingly successful therapy, is necessary to allow early treatment of new warts.

**Syringoma and chondroid syringoma**

Syringomas are common benign tumors, probably of eccrine origin, usually found around the eyelids. Ungual syringomas are extremely rare and have been reported in the great toenail bed of a 40-year-old woman presenting with onycholysis following trauma resulting in subungual hematoma. After partial nail avulsion, a tumor was discovered, adjacent to the lateral nail fold. Histology showed small tumor islands with duct lumina [70] (Fig. 21.10).

Chondroid syringoma is a benign mixed skin tumor. It is often located in the head and neck but may also
appearing around the nail. The diagnosis should be suspected as a differential diagnosis for a solid slow-growing soft tissue nodule in a finger, especially if the lesion has no contact with the underlying tendon by high-resolution ultrasound. Several cases of chondroid syringoma of the digits have been described [71–73] (Fig. 21.11), including one case of a 2.5 cm in diameter hyaline cell-rich chondroid syringoma in the tip of the left index finger of a 45-year-old female [74]. Radiography reveals impressive lytic changes with reduced technetium uptake on bone scan. Histological examination will reveal an appendageal tumor containing nests of small cuboidal cells and myxoid stroma. The lesions are termed hyaline cell-rich chondroid syringoma if the epithelial cells are predominantly plasmacytoid in nature. Malignant change is rare but has been described in a 27-year-old Japanese female with a recurrent nodule on the left great toe [75]. The treatment of the benign forms is marginal resection.

**Eccrine poroma** (Fig. 21.12)

Eccrine poroma is a benign proliferation most common on the non-hairy parts of the feet and hands. It has an anatomical predilection for the proximal nail fold [76–78]. This tumor reaches 1–3 cm in diameter, is always single, pink, and soft, and grows slowly. Typically, it is superficial, often protruding or sessile, but occasionally it may project into the dermis. It may invade the nail bed and elevate the plate [79]. When it surrounds the nail, the distal phalanx appears enlarged and the nail destroyed [80].

Two subungual eccrine poromas in female patients were described by Goettmann et al. [81]. In Richardson et al’s case, the clinical features consisted of a subungual erythematous, friable, well-defined, 6–7 mm papule under the medial aspect of the distal great toe [82].

The primary diagnosis was pyogenic granuloma since the lesions were pedunculated and one tended to bleed easily. Differential diagnosis further includes granuloma, amelanotic melanoma, wart, histiocytoma, and carcinoma. Treatment consists of surgical excision of the tumor.

---

Figure 21.10 (a) Syringoma: involvement of the lateral nail bed. Courtesy of V. Blatière. (b) Syringoma: histology.

Figure 21.11 (a) Chondroid syringoma. Courtesy of C.A. Barreto. (b) Histology of case in (a).
Spiradenoma

Spiradenoma is a benign adnexal neoplasm which classically presents in the second to fourth decades of life as a small, painful, gray to pink nodule on the upper ventral aspect of the body. An early definitive diagnosis of spiradenoma is important because malignant transformation can occur: Engel et al. [83] reported a 21-year-old man who developed a nodule on the dorsolateral aspect of his right great toe at age 9. The lesion was cauterized on several occasions and locally excised at age 13; histopathology then showed benign eccrine spiradenoma. The lesion rapidly recurred and grew very slowly until age 18 when it began to grow more rapidly. The patient eventually presented with a 40 mm bilobed painless fluctuant tumor involving the nail bed. Histological examination showed malignant degeneration in a benign eccrine spiradenoma. A 50-year-old woman presented with a splitting of the nail of her right little finger caused by a spiradenoma in the nail matrix [84]. The lesion was soft, with a gray-pink hue, and slightly tender to palpation.

Eccrine angiomatous hamartoma

Eccrine angiomatous hamartoma (EAH) is a rare, benign combined eccrine and vascular malformation usually appearing at birth or in early childhood as a slowly growing nodule or plaque predominantly involving the distal extremities, most often the backs of hands and fingers [86]. It also may present as multiple papules or hemorrhage-like maculopatches [87, 88]. Most EAH cases are asymptomatic but it may present as a suddenly enlarging and tender swelling [89, 90] or painful tumor under the nail [91, 92].

Eccrine syringofibroadenoma (Fig. 21.13)

Eccrine syringofibroadenoma of Mascaró is a rare benign tumor of the excretory portion of eccrine sweat as was shown in a 26-year-old woman with a 15-month history of a slowly enlarging papule involving the proximal nail fold of her left thumb [85]. The lesion was soft, with a gray-pink hue, and slightly tender to palpation.

(a)

(b)

Figure 21.12  (a) Eccrine poroma. Courtesy of R. Arenas. (b) Eccrine poroma: histology. Courtesy of S. Goettmann-Bonvallot.

Spiradenoma

Spiradenoma is a benign adnexal neoplasm which classically presents in the second to fourth decades of life as a small, painful, gray to pink nodule on the upper ventral aspect of the body. An early definitive diagnosis of spiradenoma is important because malignant transformation can occur: Engel et al. [83] reported a 21-year-old man who developed a nodule on the dorsolateral aspect of his right great toe at age 9. The lesion was cauterized on several occasions and locally excised at age 13; histopathology then showed benign eccrine spiradenoma. The lesion rapidly recurred and grew very slowly until age 18 when it began to grow more rapidly. The patient eventually presented with a 40 mm bilobed painless fluctuant tumor involving the nail bed. Histological examination showed malignant degeneration in a benign eccrine spiradenoma. A 50-year-old woman presented with a splitting of the nail of her right little finger caused by a spiradenoma in the nail matrix [84]. The lesion was extremely tender to touch and caused pain in the proximal nail fold region, which was suggestive of a glomus tumor. Spiradenoma may also grow in the proximal nail fold and thus induce a longitudinal groove in the nail plate,
glands [93]. Solitary syringofibroadenoma, the most common type, commonly arises in the distal region of the limbs. It usually presents as a keratotic tumor of the nail bed but can also present as an ulcerative plaque, verrucous lesion, papular or nodular lesion, or palmoplantar keratoderma. Several cases involving the nail have been reported, only in older patients, and mostly in men [94–98]. The first case was found in a man aged 61 and located in the fifth right toenail [96], the second case [97] was observed in the left ring fingernail in a 71-year-old woman suffering from pain in her finger, occasionally radiating to the wrist and intensifying with pressure. Clinically, a 2 mm-wide band ending with horny splinters was seen. Partial nail avulsion displayed keratotic filaments and red granulation tissue. The lesion was successfully removed by curettage. Histology showed anastomosing thin epithelial strands extending from the epithelium of the nail bed into the dermis. The spaces between the strands were filled with fibrovascular stroma. On the superficial level the stroma had a mucoid appearance. The anastomosing cords were made up of small and cuboidal cells with a round, deeply basophilic nucleus and scant cytoplasm. Several foci within the tumor formed duct-like structures with amorphous contents. The clear cells stained positively both with colloidal iron and alcin blue.

Periungual involvement of the great toe was shown in one of three cases of familial eccrine syringofibroadenomatosis. The skin appeared fissured and hyperkeratotic [99].

It is not clear whether solitary eccrine syringofibroadenoma is a true adnexal tumor or a reactive lesion [100]. Multiple eccrine syringofibroadenomatosis may involve the periungual tissues in association with multiple congenital abnormalities, including Schöpf syndrome [101] and odonto-onycho-dermal dysplasia [102].

Distal digital keratoacanthoma

**Definition**

Subungual and periungual keratoacanthomas (KA) are rare, benign, but rapidly growing, seemingly aggressive tumors usually situated below the edge of the nail plate or in the most distal portion of the nail bed. They have a tendency for deep invasion and bony involvement. They may occur as solitary or multiple tumors. Many cases have been reported in the literature [103–114].

**Etiology**

The pathogenesis of KA at the nail unit is still not understood. The roles of trauma [115, 116], oncogenic HPV [117], and in one case steel wool [118] have been suggested but never confirmed. In subungual KA associated with incontinentia pigmenti (IP), there is a marked dyskeratosis as observed in cutaneous lesions of the verrucous stage. This suggests an increased rate of apoptosis. Most cases of IP are caused by mutations in the nuclear factor kappa B (NF-κB) essential modulator NEMO gene, which intervenes in apoptosis regulation [119].

Keratoacanthoma is said to arise from hair follicle epithelium but there are no hair follicles in the subungual and periungual regions; this may be seen as a hint to the close relationship between hair follicle and nail apparatus and explains why some cases may be interpreted as onycholemmal cysts (E. Grosshans, personal communication) (Fig. 21.14).

Multiple KAs may appear in patients on ciclosporin [120] and suramin [121].

**Clinical features**

Clinical presentation is stereotypical: a painful distal finger/toe is associated with an underlying bony erosion on radiographs. In a review of 61 cases by Baran et al. in 2001, the tumor occurred in males in 75% of cases and predominated on the first three fingers, mostly the thumb. The great toenail was affected in one case only. Lesions were polydigital in 10 cases [115].

Keratoacanthoma is a rapidly-growing tumor (within weeks) that is always painful and most often located on the distal part of the nail bed. The lesion may start as a small and painful keratotic nodule visible beneath the free edge, growing rapidly to a 1–2 cm lesion within 4–8 weeks. Its typical gross appearance is a dome-shaped nodule with a central plug of horny material filling the crater (Fig. 21.15). The lesion rapidly plunges deeper and erodes the underlying bony phalanx. If the KA is located more proximally under the nail fold, it may present as a painful chronic paronychia: the tumor grows out from under the proximal nail fold [122], which becomes inflamed (Fig. 21.16a), and may cover or surround it with a cushion of swollen tissue (Fig. 21.16b) [123]. In women, multiple subungual KA may represent a late manifestation of IP and are termed painful subungual tumors of incontinentia pigmenti.

**Medical imaging**

Standard radiographs consistently demonstrate a well-defined, cup-shaped erosion of the underlying bone. The margins of the radiological defect show no evidence of sclerosis or any sign of periosteal reaction (Fig. 21.17) [124]. This lytic effect may be attributed to very rapid compression from the tumor rather than tumor invasion [125]. Long-term radiological follow-up of subungual KA (SUUKA) is rare. Some showed complete absence of reossification [118], others demonstrated partial reconstitution of the bony defect [126], and there is one case report of spontaneous regression with full reossification [127].

Magnetic resonance imaging (MRI) may help depict a deep infiltrating lesion of the distal nail bed. MRI is superior to radiographs in detection of an erosion of the
distal phalanx. Images show a large nodule with a homogeneous signal (intermediate signal on T1-weighted images and high signal on T2-weighted images). Intravenous injection of gadolinium provides strong peripheral enhancement suggesting an inflammatory reaction in the surrounding tissue [105]. A central area of low signal indicates the central plug of horny material filling the crater (Fig. 21.18). The limits may be ill defined because of edema in the surrounding tissues. Color Doppler ultrasound typically reveals a lesion with a heterogeneous structure, with a hypoechoic border of solid appearance and an anechoic center of fluid appearance [107].

**Differential diagnosis**

Diagnosis of distal digital KA relies on the rapid growth of the lesion and the constant pain, in association with

---

**Figure 21.14** (a) Proliferating onycholemmal cyst after surgery. (b,c) Histology of case in (a). (d) MRI of case in (a). MRI shows a large lytic lesion beneath the nail. (d) Courtesy of E. Grosshans.

**Figure 21.15** (a) Distal digital keratoacanthoma. The lesion was extremely painful. (b) Delicate clipping reveals the horny plug. (c) Distal digital keratoacanthoma of the distal bed and hyponychium.
medical imaging and histology. Its clinical differentiation from squamous cell carcinoma is nevertheless difficult (Table 21.1) [128, 129]. The three main differential diagnoses are: epidermoid implantation cyst, subungual wart, and squamous cell carcinoma. The last is also the main histological differential diagnosis, which remains difficult, and the tumor is frequently diagnosed histologically as a squamous cell carcinoma, keratoacanthoma type.

Pathology
Histology of an adequate biopsy specimen will clearly show the characteristic pattern (Table 21.2). Just as in KA of the skin, several authors believe that this tumor is only a well-differentiated variant of squamous cell carcinoma with some propensity for spontaneous regression (but not always) and low (but not absent) metastatic potential [127, 130]. Histopathology of subungual KAs may differ slightly from that of subungual squamous cell carcinoma of the skin, and the role of HPV in development of subungual KAs is not yet clear. In this particular location, the tumor is narrower but deeply infiltrating. It shows a marked shoulder with an epidermal lip, a central crater filled with keratin, and the tumor cells are large, pale, and often develop keratohyalin granules. This feature corresponds with filaggrin expression as revealed by immunohistochemistry. However, neither involucrin, cytokeratin, and filaggrin expression nor staining for the lectin peanut agglutinin allows differentiation of KA from subungual squamous cell carcinoma. Subungual KAs do not express p53 and proliferation marker Ki67 strongly whereas some, but certainly not all, subungual squamous cell carcinomas do [103, 106]. NF-κB1 and cortactin genes are amplified in subungual
Table 21.1 Difference between keratoacanthoma (KA) on the skin and under the nails [103, 106, 111, 114].

<table>
<thead>
<tr>
<th>Feature</th>
<th>KA on skin</th>
<th>Subungual KA</th>
</tr>
</thead>
<tbody>
<tr>
<td>Origin</td>
<td>Hair-bearing skin</td>
<td>Non-hair-bearing skin</td>
</tr>
<tr>
<td>Epithelial collarette</td>
<td>Present</td>
<td>Absent</td>
</tr>
<tr>
<td>Growth direction</td>
<td>More horizontal</td>
<td>More vertical</td>
</tr>
<tr>
<td>Infiltrate</td>
<td>Many neutrophils and eosinophils</td>
<td>Fewer neutrophils and eosinophils, no fibrosis at base</td>
</tr>
<tr>
<td>NF-κB1 and cortactin gene amplification</td>
<td>No</td>
<td>Yes</td>
</tr>
<tr>
<td>Ki-67 and p53 expression</td>
<td>Sometimes strong</td>
<td>Negative or weak</td>
</tr>
<tr>
<td>Bone erosion</td>
<td>Usually none</td>
<td>Rapid</td>
</tr>
<tr>
<td>Duration</td>
<td>9–12 months</td>
<td>Longer if not treated</td>
</tr>
<tr>
<td>Spontaneous regression</td>
<td>Frequent</td>
<td>Infrequent</td>
</tr>
<tr>
<td>Symptoms</td>
<td>No pain</td>
<td>Pain</td>
</tr>
</tbody>
</table>

Table 21.2 Differentiation between subungual keratoacanthoma (KA) and squamous cell carcinoma.

<table>
<thead>
<tr>
<th>Feature</th>
<th>Subungual KA</th>
<th>Subungual carcinoma</th>
</tr>
</thead>
<tbody>
<tr>
<td>Sex</td>
<td>M &gt; F</td>
<td>M &gt; F</td>
</tr>
<tr>
<td>Age (years)</td>
<td>35–65</td>
<td>60–80</td>
</tr>
<tr>
<td>Incidence</td>
<td>Very rare</td>
<td>Relatively common</td>
</tr>
<tr>
<td>Growth rate</td>
<td>Rapid (weeks)</td>
<td>Slow (months or years)</td>
</tr>
<tr>
<td>Duration of symptoms</td>
<td>Short</td>
<td>Long</td>
</tr>
<tr>
<td>History of trauma</td>
<td>Rarely</td>
<td>Sometimes</td>
</tr>
<tr>
<td>Tumor mass</td>
<td>Always present</td>
<td>Often not present</td>
</tr>
<tr>
<td>Bone invasion</td>
<td>Early</td>
<td>Late</td>
</tr>
<tr>
<td>Radiography</td>
<td>Bone erosion</td>
<td>Late bone destruction</td>
</tr>
<tr>
<td>Multiple tumors</td>
<td>Common</td>
<td>Rare</td>
</tr>
</tbody>
</table>

Adapted from Norton [141] with permission from Elsevier.

KAs but not in digital squamous cell carcinoma [103]. An antibody directed against transforming growth factor (TGF)-α was shown to give different staining patterns in KA and squamous cell carcinoma [131] but further studies are needed to establish its discriminating value. Demonstration of markers such as p53, proliferating nuclear cell antigen (PCNA), and Ki1 gives more peripheral staining in KA than in squamous cell carcinoma, but this again is not a safe differential diagnostic feature (Schulze and Haneke, unpublished data). There is no histological or immunohistochemical differentiation between subungual KAs and subungual KAs of IP [106]. If a subungual KA in a woman is confirmed, association with this genodermatosis should be excluded [132]. Histologically, perineural invasion in KA may be a risk factor for recurrence [133].

Evolution

Spontaneous regression is very unusual but has been reported [116, 127]. Reconstitution of the bony defect can be expected [125, 126]. A case of multiple familial KA [134] showed no tendency toward spontaneous involution in contrast to the case of Mittal et al. [135] associated with polyarthritis.

Management

Previous recommendations for treatment of SUKA have been divergent, ranging from conservative local excision to aggressive amputation. A review of 18 cases treated with curettage showed that 86% of lesions did not recur [126]. Thus, first-line treatment is removal of the entire tumor with curettage of the cavity [136]. Some authors suggest Mohs micrographic surgery in order to limit any risk of recurrence. However, this technique seems hardly feasible on curettage of a bony cavity [104]. Most recurrences occur within the first 5 months postoperatively, but long-term follow-up is mandatory as recurrences have been observed as late as 22 months [115, 136]. Amputation should only be considered in multiple recurrences, when massive bony destruction or a squamous cell carcinoma cannot be ruled out [115, 137]. For painful subungual tumors of incontinentia pigmenti, first-choice treatment should be acitretin 1 mg/kg/d [119].

A 51-year-old man was treated with two local infiltrations of methotrexate with a 1-week interval [109]. This resulted in tumor regression, allowing simple curettage of the residual lesion.

5-Fluorouracil has also been used, either injected into the lesion or applied as a 20% ointment three times daily for 3–4 weeks [138]. Intralosomal bleomycin may be tried in the distal nail area [139] as may methotrexate [140].
Distal digital incontinentia pigmenti tumors
Incontinentia pigmen
ti (IP), or Bloch–Sulzberger syndrome, is a multiorgan disease with an X-linked dominan
t inheritance, which affects females and usually is lethal in males. IP is caused by mutation of the IKBKG/
NEMO gene on Xq28 [142]. NEMO mutation leads to loss of function of NF-κB, a critical protein that modu
lates cellular proliferation, apoptosis, and response to proinflammatory factors, leading to the characteristic
features of IP. There are three clinical stages of skin changes: a linear erythematovesiculous and bullous reaction
which is present at birth is followed by a second stage of verrucous lesions which gradually disappear.
The third stage is characterized by a splashed or whorled pigmentation in a pattern which follows Blaschko’s lines.
Finally, these lesions may turn hypopigmented.

Ungual alterations are observed in about 40% of IP patients. Painful subungual dyskeratotic tumors (subun
gual tumors in IP) are one of the late manifestations, and appear after puberty (between the ages of 15 and 31)
(Fig. 21.19) [119, 143–146]. Usually the fingers are involved but warty brownish growths arranged linearly
along the great toes have been observed [147]. The subungual tumors tend to destroy the distal phalanx by pres
sure necrosis of the underlying bone, and they displace the nail from the nail bed, causing nail dystrophy. Partial
onycholysis often precedes the appearance of keratotic crusted papules and nodules at the distal nail bed.
Erythema and swelling of the fingertip are found at the border of the lesion. The pain is initially intermittent, but
increases in intensity and duration as the tumor enlarges.

In the proximal subungual tissue, the tumors may pro
duce a paronychia-like lesion. Drainage of firm keratina
ceous plugs or purulent debris secondary to bacterial infection may be present. The tumor may be localized
only on the proximal subungual area, or on the fold with tender swellings which are smooth proximally and warty
distally [148]. They may disappear spontaneously after several months leaving a 2 mm scar on the pulp just
under the free edge of the nail at the site of a warty lesion [148]. Hartman and Danville [149] reported the case of a
30-year-old woman with painful subungual tumors from the age of 20 years. The keratotic lesions resulted in
nail dystrophy and scalloped bone deformities of the terminal phalanges of the fingers. Regression followed
pregnancy on two occasions. Eight fingernails and one toenail were affected over a 20-year period in a woman
who developed her first lesion at 16 years of age [150]. The development of subungual squamous cell carcinoma
in subungual tumors in IP has been reported [151] but malignant degeneration is a matter of debate [152].

Histological examination of the tumors shows a verrucous or pseudoepitheliomatous hyperplasia of the epidermis with hyperkeratosis and hypergranulosis where dyskeratotic cells are found at all levels thus resembling the second stage of IP development. Differential diagnoses include warts, epidermoid cysts, subungual fibromas, squamous cell carcinoma, and above all keratoacanthoma, which is clinically and often also histologically indistinguishable [106, 116].

Despite possible self-healing, the patient asks for treatment because of the intense pain [153] and disability. Management by desiccation and curettage or surgical excision is usually successful but permanent nail atrophy may occur. A course of systemic retinoids should be considered despite possible recurrence [154]. Malvehy et al. [155] gave 1 mg etretinate per kg bodyweight and produced a rapid response with resolution of pain and marked reduction of the lesion, including improvement of the bony alterations and nail deformity. Also some success has been achieved with intralesional 5-fluorouracil injection [119].

Longitudinal subungual acanthoma (subungual seborrheic keratosis, subungual linear keratotic melanonychia)
Subungual seborrheic keratosis is a rare lesion which may present principally as a longitudinal melanonychia
(Fig. 21.20a) that may mimic a foreign body or a longitudi
dinal leukoxanthonychia [156–159]. Both types can be
associated with pachyonychia [158, 160, 161].

Longitudinal melanonychia displaying features of keratinized acanthoma was described in two patients in
1999 [156]. In both cases, a pigmented band consisted of a subungual keratinized epithelial ridge involving nail bed and distal lunula (Fig. 21.20b). The origin of the pigment is linked to its synthesis within the acanthoma of the nail bed. Interestingly, these lesions were remi
niscent of seborrheic keratosis without cell whorls, but with pigmentation mimicking the melano-acanthoma of
Mishima and Pinkus, a variety of pseudoseborrheic keratosis observed in colored people. The second clinical

Figure 21.19 (a) Subungual incontinentia pigmenti tumor. (b) Dyskeratotic cells of case in (a). Courtesy of J. Mascaro.
presentation with longitudinal leucoxanthonychia may resemble onychomatricoma (Fig. 21.21a,b) but dermoscopically shows longitudinal filiform globular hemorrhages and milia-like cysts which are also evident on frontal view of the nail plate free edge.

On pathological examination, onychocytic matricoma resembles an irritated seborrheic keratosis (Fig. 21.22), with an endophytic proliferation of primarily basaloid cells and several zones displaying squamous eddies. However, the squamous eddies are composed of larger pale pink cells arranged in an onion ring fashion, representing the matrix prekeratogenous zone, with central eosinophilic collections representing the matrix keratogenous zone. There are only minimal dermal changes. In nail bed acanthoma, the pathological appearance is very close to an acanthotic seborrheic keratosis with or without horn cysts [162].
Considering the similarities between subungual seborrheic keratosis and onychocytic matricoma, some authors speculated that they are likely two entities belonging to a single spectrum of disease: nail unit acanthoma [163]. Surgical treatment and histological examination must be performed to exclude malignant lesions.

Localized multinucleate distal subungual keratosis [164] (Fig. 21.23)
Distal subungual keratosis with occasional dyskeratotic cells is a small horny lesion originating from the hyponychium region, resembling a forme fruste of distal subungual fibrokeratoma. It may be followed clinically and histologically as far as the lunula and is well demonstrated by MRI. Baran and Perrin [165] found multinucleate giant cells in several of these lesions, and have therefore suggested that the term localized multinucleate distal subungual keratosis should be replaced by “onychopapilloma” (nail-producing papilloma). Gee et al. [166] consider that onychopapilloma is a useful descriptive term but that the histology may be variable from one case to another. However, no new cases of localized multinucleate distal subungual keratosis have been published since then.

Onychopapilloma of the nail bed (subungual keratosis with longitudinal erythronychia first described as “acquired subungual superficial capillary malformation”) [165]
Onychopapilloma was first reported in 1995 by Baran and Perrin [164]. It is a benign nail tumor of the distal nail matrix and the nail bed that presents as a monodactylous linear streak under the nail plate. Linear erythronychia [167] (Fig. 21.24), linear leukonychia [168] (Fig. 21.25a,b), or linear melanonychia [169, 170] (Fig. 21.26) are all clinical signs seen in onychopapilloma. The streak frequently

Figure 21.23 Distal subungual keratosis with multinucleation. Courtesy of A. Villaneva.

Figure 21.24 Onychopapilloma of the nail bed showing as longitudinal erythronychia. Courtesy of M. Henry.

Figure 21.25 Onychopapilloma presenting as a longitudinal leukonychia. Note the distal onycholysis with hemorrhages. (b) Onychopapilloma presenting as a longitudinal leukonychia: dermoscopic aspect.

Figure 21.26 Onychopapilloma presenting as a longitudinal melanonychia.
has interrupted splinter haemorrhages, and distally it ends in a visible hyperkeratotic plug that sticks out from under the nail plate. The nail plate often shows distal splitting, a wedge-shaped notch, and associated localized onycholysis. In some rare instances, there may be two onychopapillomas on the same nail (Fig. 21.27) and some patients may exhibit onychopapillomas on several nails (Fig. 21.28). Tosti et al. [171] reviewed 47 cases of onychopapilloma. The most common clinical presentation was longitudinal erythronychia, followed by longitudinal leukonychia, longitudinal melanonychia, long splinter hemorrhages without erythronychia, leukonychia, or melanonychia, and short splinter hemorrhages without erythronychia, leukonychia, or melanonychia. A focal subungual mass is highly suggestive for the diagnosis and was present in all 47 cases. Distal fissuring was observed in 11 cases.

The hyperkeratotic plug at the distal end of the nail is often painful when pulled or clipped. Dermoscopy (Fig. 21.29) more precisely shows the distal subungual hyperkeratosis, the “hairpin-like” vessels, and, when present, the subungual splinter hemorrhages.

Baran and Perrin biopsied longitudinal erythronychia in 16 subjects showing an onychopapilloma in 14 cases and squamous cell carcinoma (SCC) in the remaining two [165]. Jellinek and Lipner [172] did the same in 61 patients presenting with localized longitudinal erythronychia. Onychopapilloma was diagnosed in 41 (67%) of these cases of localized longitudinal erythronychia. Malignancy was identified in three of 61 cases (in situ squamous cell carcinoma in two and melanoma in one).

The diagnosis onychopapilloma can be confirmed histo logically following excision of the lesion but also from a nail clipping which includes the localized asymmetric keratotic portion underneath the free edge of the nail [165, 171]. In all cases of Baran and Perrin of “onychopapilloma”, nail bed acanthosis and papillomatosis were evident, and were combined with a keratogenous zone identical to the nail matrix [165]. In addition, they found multinucleate giant cells in four onychopapillomas. In two cases, dysplasia amounting to squamous cell carcinoma in situ was found in the absence of any other diagnosis or as a part of Darier disease. The presentation of SCC in this pattern has not been previously reported but nail bed lichen planus was found to be associated with onychopapilloma in a 19-year-old woman [173].

Management of monodactylous longitudinal streaks with subungual hyperkeratosis should be based on the patient’s symptoms or changes in the lesion. Symptomatic
Tumors of the Nail Apparatus and Adjacent Tissues

lesions should be surgically excised. Sudden onset or changing streaks should be excised to rule out Bowen disease and other causes of linear erythronychia [174]. Stable streaks can be reevaluated in a few months. Punch biopsies can miss the diagnostic pathology or contribute to the recurrence of a lesion if only a portion of the tumor is sampled. Complete excision with a longitudinal nail unit biopsy from matrix to hyponychium that includes the length of the lesion is recommended for these lesions [167].

**Acantholytic dyskeratotic acanthoma**

Acantholytic dyskeratosis is a histological pattern defined by a hyperkeratotic and parakeratotic epidermis with intraepidermal clefts containing acantholytic and dyskeratotic keratinocytes. It is usually an accidental finding in histology and resembles Darier disease or warty dyskeratoma but reflects a different tumorous process.

Three cases involving the nail have been reported, of which two were in children [175]. Both presented as median longitudinal hemorrhagic lesions in the thumbs (Fig. 21.30), originating from the matrix and extending up to the distal part of the nail apparatus. This was accompanied by onycholysis and resembled onychopapilloma.

**Subungual warty dyskeratoma**

Monodactylous longitudinal erythronychia was the presenting sign of Higashi’s patient [176].

A longitudinal reddish ridge was seen in the left third fingernail of a 73-year-old man. Originating in the lunula, it was bordered by splinter hemorrhages and eventually caused a red line. The nail plate was slightly fissured at its free margin (Fig. 21.31). Nail avulsion revealed a longitudinal ridge in the nail bed. Histology showed nail bed papillomatosis with long thin digitations penetrating the underlying connective tissue almost horizontally. Numerous multinucleate cells were seen. A crateriform impression existed at the hyponychium with epithelial digitations containing dyskeratotic cells, corps ronds, and grains as well as suprabasal acantholysis [177]. Almost identical lesions, but not as focal as in this case, can be seen in dyskeratosis follicularis of Darier.

**Verrucous epidermal nevus**

Involvement of the distal phalanx and nails by verrucous epidermal nevi is rare. They may be congenital or late-onset lesions. The history and linear arrangement usually enable easy differentiation from extensive warts. They should be taken into consideration if both the nail fold and the corresponding nail are involved.

Verrucous epidermal nevi are as a rule asymptomatic, except when they impinge upon the proximal nail fold, where they may cause recurrent paronychia and distort the nail [178].

![Figure 21.30](image1.png)  
**Figure 21.30** Acantholytic dyskeratotic acanthoma presenting as a median longitudinal hemorrhagic lesion.

![Figure 21.31](image2.png)  
**Figure 21.31** (a) Longitudinal erythronychia (arrow) caused by warty dyskeratoma. (b) Histology in the hyponychium area. Courtesy of N. Higashi.
Involvement of the nail bed causes ridging, splitting, discoloration, or dystrophy (Fig. 21.32). Any linear verrucous epidermal nevus whether with or without granular degeneration (epidermolytic hyperkeratosis) may affect the nail.

Histopathology shows papillomatosis with hyperkeratosis giving a wart-like appearance. However, HPV-characteristic cytopathic effects are lacking. In the matrix and nail bed, the typical epithelium is no longer discernible and the verrucous nevus does not produce a normal nail plate. A clinically similar aspect was seen in a 3-year-old girl with a porokeratotic eccrine duct nevus affecting the periungual skin of her fifth right toe [179]. Differential diagnosis includes lichen striatus and inflammatory linear verrucous epidermal nevus (Fig. 21.33). In the nail unit, inflammatory linear verrucous epidermal nevus [180, 181] and epidermal nevi in CHILD (congenital hemidysplasia with ichthyosiform erythroderma and limb defects) syndrome have been reported in both pediatric and adult patients [182, 183]. The surrounding skin may be treated with excision and grafting [181] but the involved nail plate will not profit from this.

Nail cysts
The nail cysts represent a broad group of lesions that differ in histogenesis and clinical picture. They may be small and subclinical, such as subungual epidermoid inclusions (which are discussed in the next section). Others are indistinguishable from epidermal inclusion cysts of the skin and are known as implantation epidermoid cysts [184] (synonyms: keratin inclusion, squamous epithelial or traumatic cysts). Finally, some cysts may contain epithelium that resembles that of the nail bed and are called onycholemmal cysts [185]. Subungual onycholemmal cysts may present with a wide spectrum of clinical findings including marked subungual hyperkeratosis, onychodystrophy, ridging, nail bed pigmentation, clubbing, thickening, or less often a normal-appearing nail [186]. They may also mimic subungual melanoma [186].

Implantation epidermoid cysts
Etiology
Postoperative implantation epidermoid cysts may occur in the proximity of scars (Fig. 21.34a) and often follow surgery for ingrown toenail [187, 188] or realignment procedures in children [184]. They may also be secondary to heavy or penetrating trauma (Fig. 21.34b), with implantation of epidermis into subcutaneous tissue or even into the bone (Fig. 21.34c); the trauma may have
occurred long ago (even decades) and may not always be remembered.

**Evolution**

The implanted epithelial cells continue to regenerate, creating a cyst in the subcutaneous tissues or the bone. As the cyst expands, first medullary and cortical bone are eroded, creating a change of the dorsal surface of the distal phalanx and a resultant deformity of the nail bed and nail. Persisting discomfort after surgery at the nail unit may warrant investigation by radiography or MRI since an intraosseous implantation epidermoid cyst can be a late complication or an underlying condition [189].

**Clinical features**

Pain and swelling of the terminal phalanx are the most frequent clinical signs [190]. Tenderness or pain are of late onset, result from compression of the bone, and may eventually result in a fracture. Shooting pain was described in one case, where there was soft tissue involvement alone [191]. Acquired pincer nail is an unusual presentation [192] (Fig. 21.35). Dermoscopically the “eclipse sign” has been used to describe the peculiar aspect of an implantation epidermoid cyst seen through the nail plate with a ring-shaped aspect [193]. Phalangeal intraosseous implantation epidermoid cysts occur twice as frequently in men as in women and the left hand is more often affected than the right [194].

**Medical imaging**

Early in the disease, bone erosion is absent or subtle and not visible on radiographs. Later the lesion appears as a round, osteolytic zone embedded in the distal phalanx, without trabeculae and sclerosis (cf. enchondroma), or as a marginal defect of the cortical substance of bone [188, 195] (Fig. 21.34c). Sclerosis may however be present in some cases [190]. The clinical and radiological differential diagnosis may be very difficult [196]. Rarely, the cyst may contain a penetrating foreign body [197]. MRI shows a regular mass with homogeneous or slightly heterogeneous content and intermediate signal on T1- and T2-weighted images. A heterogeneous enhancement is noted after injection of gadolinium. The thin epidermal layer is depicted as a regular rim with a high signal identical to that of normal epidermis. Bone erosions, even when subtle, are easily detected on axial images. The area of an old penetrating injury may be marked by dark artifacts on gradient echo images.

**Differential diagnosis**

Differential diagnosis comprises virtually all lesions, both reactive and neoplastic, that can cause swelling of the terminal phalanx [198].

**Pathology**

Histopathology shows a simple epidermoid cyst filled with orthokeratin and lined by a thin epidermis. However, if remnants of matrix epithelium were displaced into the subcutaneous tissue, these matrix cysts may also contain areas exactly resembling epithelial lining like the nail matrix. Usually matrix cysts are hybrid and contain both

---

**Figure 21.34** (a) Postoperative implantation cyst in the posterolateral nail fold. (b) Posttraumatic implantation cyst. Pain was intense. (c) Radiograph of case shown in (b).

**Figure 21.35** (a) Pincer nail deformity due to epidermoid cyst. (b) Intraosseous epidermoid cyst: histological changes.
epidermoid and matrix-like lining but pure matrix cysts may occasionally also be encountered [17]. Matrix cysts are also usually seen after inadequate wedge excision for ingrown toenails.

**Management**

Treatment is curettage of the cyst and its lining, allowing the defect to fill on its own or, if it is large, using a medullary bone graft to fill the defect and give support to the nail bed. Depending on the location of the cyst, the surgical approach may be through a lateral incision or, as in Fig. 21.36, a fish-mouth incision around the tip of the finger laying the nail and matrix back to treat the cyst.

**Onycholemmal cysts (subungual epidermoid inclusions)**

Onycholemmal cysts, also called subungual epidermoid inclusions, are a relatively frequent finding in many nail biopsies and excision specimens. No pathognomonic clinical alterations exist: the nail may look normal or be thickened, dystrophic, ridged, or yellow, or the nail bed may appear hyperkeratotic. One case even mimicked a subungual melanoma [186]. The diagnosis is made by histopathology. There are small epithelial inclusions, sometimes solid but mostly with central keratinization of the onycholemmal type without a granular layer. Secondary calcification is common [199]. Sometimes, the onycholemmal cysts are seen to derive from elongated rete ridges of the nail bed epithelium. The relationship of calcified onycholemmal cysts to the subungual calcifications seen in elderly persons is not yet clear.

Multiple subungual epidermoid inclusions (epidermal buds [79]) develop from the ridges of the nail bed epithelium. Although their lining is histologically identical with subungual onycholemmal cysts, they usually remain microscopic. Exceptionally they become large enough to produce symptoms, such as swelling of the nail bed resulting in subungual keratosis, onycholysis, or a dystrophic nail plate [199, 200]. Initially, this is painless but later mild pain may appear due to compression between nail and bone. Trauma is a possible cause in some instances [201] and has been reported as the cause of bilateral inclusions on great toes in a barefoot patient [202].

In addition to the two main varieties, eight cases of another type of subungual epidermoid inclusion have been reported [203]. The most striking clinical features are subungual hyperkeratosis associated with shortened and dystrophic nail plates (Fig. 21.37). Onycholysis was observed in one case.

![Figure 21.36](a) Enlarging painful fingertip several years following the injury. (b) Radiograph shows erosion of the bone of the distal phalanx. (c) The nail and nail bed are elevated as a flap, revealing the bone cyst which is curetted. (d) The defect in the bone is filled with medullary bone from the distal radius. (e) The fingertip is returning to normal 1 year later and is no longer painful. © E. Zook.
There is no pathognomonic clinical or radiological sign for subungual epidermoid inclusions. A nail bed biopsy is required for diagnosis because the reported inclusions are microscopic rather than macroscopic. In all cases, biopsy shows marked hyperplasia of the nail bed and epidermoid cysts in the dermis (Fig. 21.37). Once the diagnosis of subungual epidermoid inclusions has been made, no treatment is clearly curative, although simply making an accurate diagnosis may prevent inappropriate treatment [199]. Onychomycosis and psoriasis are the main differential diagnoses.

Fibroepithelial tumors
- Fibrokeratomas (see the section on “Soft tissue tumors/Acquired ungual fibrokeratoma” in this chapter).
- Invaginated fibrokeratoma (see the section on “Soft tissue tumors/Invaginated fibrokeratoma” in this chapter).

Acquired monodactylous longitudinal pachyonychia
This term describes longitudinal thickening of the nail plate and a yellow discoloration or a black pigmentation [159]. It encompasses three onychomatrical tumors that form a thick nail plate: (i) onychomatricoma (OM), (ii) onychocytic matricoma (OCM), and (iii) onychocytic carcinoma (OC).

Onychomatricoma
Onychomatricoma (OM) is a rare benign tumor of the matrix, first described by Baran and Kint under the term onychomatrixoma [204]. Similar tumors of the nail matrix have also been reported as “onychoblastoma,” “unguioblastoma,” and “unguioblastic fibroma” [205, 206]. OM was identified as an uncommon benign tumor specific to the nail apparatus [204, 207, 208]. Hundreds of cases have now been identified [208–216]. This typical tumor is formed by fibroepithelial digitations emerging from the matrix. Those digitations are onychogenic and responsible for the thickening of the nail plate and consequently xanthonychia.

Etiology
The etiology is unknown. Whether OM is a true benign neoplasm or a reactive proliferation is not yet clear. Recently, Lee [217] suggested that OM might derive from the onychodermis because CD10, a marker of the onychodermis, is expressed in the stroma of OM.

Epidemiology
The vast majority of cases were reported in white people, especially in Europe. Only one patient was black [218]. The mean age of presentation is approximately 51 years [219]. Only one case has been reported in a child on a clinical basis but as no surgery was performed there is no confirmation of the diagnosis [220].

Clinical features
Onychomatricoma is a slow-growing, painless tumor and most patients seek medical care years after onset, mostly for cosmetic or functional concerns. The tumor affects mainly the finger (75%) and involves the middle finger in two-thirds of cases [221]. Some cases have been reported on the lesser toes [222, 223] and exceptional cases involved several digits [204].

Several clinical signs are striking enough to either make the diagnosis or at least to arouse suspicion:
- thickening of the nail plate, of various width, often sparing a part of normal, pinkish nail
- transverse and longitudinal overcurvature of the affected portion of the nail
- leukoxanthonychia of the affected part of the nail
- longitudinal ridging, sometimes quite prominent on the surface of the nail (Fig. 21.38)
● splinter hemorrhages, mostly proximal but sometimes distal
● honeycomb cavities at the frontal margin of the thickened nail plate [224].

A nodule may be seen at the base of the longitudinal nail dystrophy [225] (Fig. 21.39). Unusual clinical variants have been described: a giant form (Fig. 21.40) [226], an association with dorsal pterygium (Fig. 21.41) [227, 228], and longitudinal melanonychia [229] (Fig. 21.42). It is not uncommon for patients with onychomatricoma to develop coexisting onychomycosis, as channels created by the tumor render the nail plate susceptible to invasion by fungi (Fig. 21.41) [230–232]. Exceptionally, the length of the matrical digitations is such that clipping of the free edge induces bleeding [212]. In some rare instances, the OM is completely separated from the nail plate, showing as a lateral cutaneous horn (Fig. 21.43). Histological examination establishes the diagnosis by showing the classical pattern of a "panonychoma fibropapilliferum" [211, 233].

Lesort et al. [215] studied 34 patients in order to define preoperative diagnostic criteria using non-invasive investigations: observation and dermoscopy (Fig. 21.44a).
For clinical criteria, the highest mean values were for leukonychia, splinter hemorrhages, and thickening of the plate (Table 21.3). Dermoscopic criteria, such as longitudinal parallel white lines, parallel lesion edges, splinter hemorrhages, dark dots, free-edge nail pitting, and thickening of the free edge, were more often found to be present.

### Diagnosis

The diagnosis can be confirmed with imaging methods including ultrasound and MRI and nail clipping. Dermoscopy helps in diagnosis by showing multiple perforations of the nail plate at its free border (Fig. 21.44b). In 2011, Miteva et al. showed that analysis of nail clipping is a fast, minimally invasive method to achieve the correct diagnosis of onychomatricoma and also very useful to differentiate onychomatricoma from subungual tumors and to exclude fungal infection by a periodic acid–Schiff (PAS) stain [234].

Nail avulsion is diagnostic as it exposes a villous tumor that evokes a sea anemone. The proximal nail appears as a thickened funnel, storing filamentous digitations of matrix fitting into the holes of the proximal nail extremity (Fig. 21.45).

### Table 21.3 Hallmark clinical and dermoscopic signs of onychomatricoma [215].

<table>
<thead>
<tr>
<th>Naked eye observation</th>
<th>Dermoscopic examination</th>
</tr>
</thead>
<tbody>
<tr>
<td>Leukonychia</td>
<td>Longitudinal parallel white lines</td>
</tr>
<tr>
<td>Splinter hemorrhages</td>
<td>Splinter hemorrhages</td>
</tr>
<tr>
<td></td>
<td>Dark dots</td>
</tr>
<tr>
<td>Thickening of the affected nail plate</td>
<td>Woodworm aspect of the free edge</td>
</tr>
<tr>
<td></td>
<td>Thickening of the free edge</td>
</tr>
</tbody>
</table>

For clinical criteria, the highest mean values were for leukonychia, splinter hemorrhages, and thickening of the plate (Table 21.3). Dermoscopic criteria, such as longitudinal parallel white lines, parallel lesion edges, splinter hemorrhages, dark dots, free-edge nail pitting, and thickening of the free edge, were more often found to be present.

### Figure 21.42
Onychomatricoma. Pigmented variant. Courtesy of G. Tassara.

### Figure 21.43
Onychomatricoma. Variant presenting as a lateral horn.

### Figure 21.44
Onychomatricoma. Dermoscopy: (a) upper nail; (b) free edge revealing woodworm features.
Differential diagnosis
The clinical features are characteristic but onychomycosis and Bowen disease [111] should be ruled out.

Medical imaging
Ultrasound shows the tumoral lesion as a hypoechogenic area affecting the nail matrix and a hyperechogenic area corresponding to the digitiform (or fingerlike) projections [235].

Magnetic resonance images are typical [236, 237]. Sagittal images highlight the tumoral core in the matrix area and the invagination of the lesion into the funnel-shaped nail plate. The center shows a low signal on all images with a peripheral rim with a signal identical to that of normal epidermis (Fig. 21.46). The distal filamentous extensions present a higher signal on T2-weighted images due to a mucoid stroma with high water content. Axial slices accurately show the holes in the substance of the nail plate, filled with the filamentous extensions.

Pathology
On nail clippings, OM is seen as a thickened nail plate showing lacunae of different sizes and shapes filled with serous fluid and lined by a thin layer of epithelium (Fig. 21.47) [234]. The epithelial proliferations are clearly highlighted with the cytokeratin stain. Nail clipping is also very useful to differentiate OM from subungual tumors and to exclude fungal infection by a PAS stain.

This fibroepithelial tumor consists of two anatomical zones; three histological criteria are used for each one [211, 233]. The proximal zone is located beneath the proximal nail fold with a proximal border starting at the root of the nail and a distal border corresponding to the cuticle. It is characterized by: (i) deep epithelial invaginations filled with a thick V-shaped keratogenous zone; (ii) a thickened
Tumors of the Nail Apparatus and Adjacent Tissues

- multiple “glove finger” digitations lined with matrix epithelium oriented around antero-oblique connective tissue axes
- perforation of the nail plate by multiple cavities that, generally at the distal edge of the lunula, lose their epithelial digitations and become filled with serous fluid
- the connective tissue stroma of the digitations extending deeply into the dermis and not demarcated from healthy tissue.

The loose and vascular stroma of these epithelial digitations explains the proximal splinter hemorrhages seen clinically. The yellow color of the nail plate from lunula to hyponychium is caused by thickening of the nail as a result of the keratogenous layers surrounding these digitations.

In 2010 Perrin et al. [238] introduced new clinical and histological features by which they were able to distinguish several and sometimes misleading types of OM. The morphology of the nail plate is crucial for the diagnosis, but when the nail plate is not available, immunohistochemistry can aid diagnosis by highlighting the peculiar immunophenotype of OM, which expresses CD34 but not CD99, epithelial membrane antigen, S-100 protein, actin, and desmin. Immunohistochemistry using the proliferation marker Ki-67 (MIB-1) showed only a low proliferation rate [209]. The tumor may be considered as the result of disturbed differentiation of nail matrix cells.

The differential diagnosis between OM, OCM, and OC can also be made upon histological grounds [233]. OM is a fibroepithelial matrical tumor generating a thick nail plate with multiple fibrous villous projections. Similar to OCM and OC, it has a thin basaloid compartment with alternation of prominent epithelial digitations and invaginations. However, no findings are present of OCM with spheres of onychocytes at the proximal part of the tumor. Most importantly, OM presents with a prominent fibrous stroma which is absent in OCM and OC.

Two other histological differential diagnoses can be discussed [211].

- In longitudinal sections the structure is reminiscent of a fibrokeratoma. However, a diagnosis of fibrokeratoma of the nail matrix can be excluded on the basis of the multiplicity of fibroepithelial digitations, absence of a horny corn, and, at the distal border of the thickened nail plate, the presence of cavitations filled with serous fluid.
- The stroma of the lunular segment of the OM can suggest a fibroma. However, the latter can be ruled out on the basis of the hyperplastic and onychogenic nature of the epithelium. Histologically, an ungual fibroma compresses and thins the matrix epithelium which results clinically in thinning of the nail plate in the form of a longitudinal groove.

Examination by electron microscopy [239] shows basal cells in the proximal zone of the OM with various features, some being lacunar while others have only a limited cytoplasmic rim containing mitochondria and tonofilaments. In the parakeratotic cell columns, the cells elongate and homogenized tonofilaments appear. Around the lacunae the cells are poorly differentiated and their cytoplasm is granular. It can be concluded that the basal cells have a decreased number of tonofilaments and desmosomes and that their evolution is not uniform.

**Management**

Surgical removal of the tumor is the only option. The tumor should only be shaved [240]. As it is impossible to replace the plate (which is altered and should undergo histological examination) it might be wise to slide some tulle gras under the proximal nail fold to avoid any adherence between the ventral part of the proximal nail fold and the matrix which may result in pterygium.

**Onychocytic matricoma and onychocytic carcinoma**

Onychocytic matricoma is a recently described rare tumor of the nail matrix. It is a benign acanthoma of the nail matrix producing onychocytes [159]. Clinically, the lesions were described as monodactylous longitudinal melanonychia. Therefore, its clinical importance is as a benign mimicker of subungual malignant melanoma and Bowen disease [241] but it may also mimic a foreign body [158]. One case of a hypopigmented onychocytic matricoma was published [163]. The pathology is reminiscent of that of subungual seborrheic keratosis, which is probably a variant of the same entity [163]. Nail clippings of onychocytic matricoma in four patients [233] showed a localized longitudinal band pattern of a thickened nail plate with yellow discoloration in two cases and a black streak in two cases. All cases showed a V-shaped keratogenous epithelial tumor with a papillomatous pattern of growth. The nail plate was thickened with small holes in a honeycomb pattern. In contrast, the four onychomatricomas in this study showed the classical pattern of a true onychomatricoma.

Onychocytic carcinoma is the malignant counterpart of onychocytic matricoma [242]. The key feature of active production of a thick nail plate by the neoplastic matrical epithelium permits easy differentiation of onychocytic carcinoma from subungual Bowen disease. Clinically, patients present with longitudinal yellowish thickening of the nail plate or faint melanonychia with splinter hemorrhages. Four patients, aged 36 to 53 years old, with this entity have been described [242–244], although it has been suggested that the case of Wang et al. might have had a periangual sweat gland carcinoma with destruction of the nail bed [244].

Given the peculiar thickening of the nail plate observed in onychomatricoma, onychocytic matricoma, and onychocytic carcinoma, a distinctive new type of nail band pattern, termed acquired localized (monodactylous) longitudinal pachyonychia, was proposed [159].
Premalignant lesions

Actinic keratosis and arsenical keratosis

Actinic keratoses are the most common precancerous lesions of the skin. The nail provides near-complete protection of the nail bed from ultraviolet light [245], and actinic keratoses seem to be exceptionally rare in the subungual area despite the occurrence of subungual keratoacanthoma and squamous cell carcinoma [141]. They usually present as cutaneous “horns” on the proximal nail fold. Since, however, only about one-third of cutaneous horns overlie actinic keratoses, each lesion must be biopsied or completely excised. Common warts, Bowen disease, squamous cell carcinoma, chronic radiodermatitis, arsenical keratoses, and keratoacanthoma may also give rise to cutaneous horns.

Arsenical keratoses are due to a high content of arsenic in water or wine, or to iatrogenic arsenic ingestion. Exposure of the general population remains problematic in several areas of south-east Asia. Microscopically, they cannot definitively be differentiated from other types of keratoses such as actinic keratoses; however, they lack the actinic elastosis associated with an actinic keratosis. Keratotic papules and plaques develop on the periungual skin or nail bed. The latter may also become diffusely hyperkeratotic. Nail dystrophy subsequently develops. All patients with signs of chronic arsenical poisoning must be carefully examined and followed up, since arsenic has a high carcinogenic potential for various organs.

Radiodermatitis (Figs 21.48–21.51)

Acute radiodermatitis results from gross overdosages, accidental or therapeutic. Marked painful edema with erythema and vesication develops and a peculiar bluish pigmentation of the nails is commonly noted [246]. In more severe instances, the nails may be shed, permanently or temporarily [247], or may become deformed and defective.

Acute necrosis of the fingertip, nail apparatus, and distal phalanx can occur from massive radiation overdose. Chronic effects have been seen after the treatment of eczema, psoriasis, onychomycosis, and warts, and in healthcare workers before the institution of proper precautions [1].

Chronic radiodermatitis [248] can be caused by ionizing radiation which may lead to skin cancer up to 30 years after exposure. The earliest signs are longitudinal ridging and brittleness. Later, the surrounding skin appears sclerotic and atrophic with telangiectasia and hyperkeratosis.
Ulceration may occur and is slow or impossible to cure. The nail plate becomes dull and slightly opaque with a brownish hue. A hyperkeratotic black mass of the distal nail bed due to increased dermal capillaries in a sclerotic connective tissue has been found to be associated with pseudoclubbing [249]. Involved nails become variably thickened or distorted with splitting of the distal edges [250]. The nail bed may develop fine, red longitudinal striations which proceed to form punctate charcoal patches. A verrucous lesion appearing on the hyponychium or adjacent nail bed may herald malignant degeneration. A case of Merkel cell carcinoma with squamous cell carcinoma arising in chronic radiodermatitis of a finger has been reported in a gastroenterological surgeon who had frequently performed digestive tract radiography using naked hands for over 50 years [250]. Also an ulcerated basal cell carcinoma occurring on the proximal nail fold of a respiratory specialist [251] and a periungual porocarcinoma in another healthcare worker [252] were supposed to be induced by chronic exposure to ionizing radiation. A case of Merkel cell carcinoma with squamous cell carcinoma arising in chronic radiodermatitis of a finger has been reported in a gastroenterological surgeon who had frequently performed digestive tract radiography using naked hands for over 50 years [250]. Also an ulcerated basal cell carcinoma occurring on the proximal nail fold of a respiratory specialist [251] and a periungual porocarcinoma in another healthcare worker [252] were supposed to be induced by chronic exposure to ionizing radiation. Hyperkeratosis of the nail bed elevates the nail and causes pain. It may be associated with onycholysis and leukonychia [253]. Paronychia-like flares are the rule. Occupational radiodermatitis from iridium-192 exposure was reported from Spain [254]. After an acute episode, an asymptomatic period of several months may follow before the typical picture of chronic radiodermatitis appears. Similar lesions also occurred after exposure to radioactivity from the nuclear plant explosion at Chernobyl.

Treatment depends on the size and location of the keratotic lesions. For small nail bed lesions, curettage may be efficient after a U-shaped piece of the distal nail has been removed. En bloc excision of the nail apparatus with healing by secondary intention [255] or Mohs fresh tissue technique which spares the normal surrounding tissue are treatments of choice. The defect can be covered with a free graft or a flap [256] or left to heal by secondary intention. Imiquimod was used for conservative treatment of mild cases.

Malignant epithelial tumors

When dealing with malignant nail tumors, five features should always be taken into account:

- variation in nail color
- nail plate deformity
- partial or total disappearance of the nail plate
- pain
- periungual soft tissue abnormality.

Squamous cell carcinoma and Bowen disease of the nail apparatus

Definition

Squamous cell carcinoma (SCC) is the most frequent malignant tumor of the nail apparatus, where presentation as in situ SCC (also termed Bowen disease) is more common than invasive SCC.

Epidemiology

Bowen disease has been reported in individuals between the ages of 4 [257] and 90, the incidence being highest in the 50–79 year range [258]. Three-quarters of cases occur in males [259–261]. Invasive and metastasizing squamous cell carcinomas have been reported in individuals from the age of 10 years [262, 263].

Pathogenesis

Most cases of Bowen disease of the periungual region may arise within the context of HPV infection [6, 264–273]. There is a particular link with HPV 16, 18, 34, 35, 52, 58, and 73 [4–6, 274–277]. Serotype 16 is isolated in three-quarters of cases [260]. One-third of patients with SCC of the nail apparatus have a personal history of HPV-associated genital disease (genital warts, dysplasia, or cancer of the cervix) or a similar history in a sexual partner. The average time between the onset of the genital disease and the appearance of the nail tumor is around 12 years [260]. This finding prompts one to speculate whether genital–digital transmission of the virus occurs. In Rudlinger et al’s case [276], Bowen disease of the nail apparatus and the Bowenoid papulosis of the anogenital area revealed an identical HPV 35 infection. As the patient suffered from long-lasting pruritus of the anogenital area, scratching may have resulted in autoinoculation. Similarly, HPV 16 genome from digital Bowen
disease of two women was identical with HPV DNA from archival samples of their genital dysplasia [272]. However, in the case of Bowen disease reported by Ostrow et al. [278], the HPV 16 DNA was discovered in a solitary subungual warty lesion and the integration of the HPV 16 DNA appears (so far) to be closely associated with the progression of a premalignant lesion to a malignant one. Cytophotometric analysis of a case of bilateral subungual Bowen disease with HPV 16 suggested a lack of HPV 16 genome integration into the host DNA of squamous cell carcinoma [271]. There is no reason to assume that benign viral warts undergo malignant transformation.

Other etiological factors may include arsenic, for example in elderly patients with psoriasis. Trauma, infection, pesticides, subungual tumors of incontinentia pigmenti [151, 152], and chronic paronychia [279, 280] but, above all, exposure to X-irradiation (physicians, dentists, patients) have been cited as etiological factors. This may be followed by radiodermatitis [255] which, with the discovery of HPV infection, is the most common factor for the development of squamous cell carcinoma [274].

**Clinical features**

The fingers are significantly more frequently affected than the toes [281, 282]. The largest published series identifies the right index and middle fingers as the most commonly affected. This finding is in agreement with the postulated genital–digital transmission of HPV [259]. The tumor grows slowly and the duration of signs and symptoms from onset to the time of diagnosis has varied from several months to 30 years [283]. The neoplastic process most commonly originates in the nail folds or nail grooves but also may develop in the subungual tissues. Periungual involvement includes hyperkeratotic or papillomatous or fibrokeratoma-like growth [284] which may also occur in a subungual location [285]; erosions, scaling, and fissuring of the nail folds; whitish cuticle [79]; periungual swelling from deep tumor proliferation, with erythema caused by inflammation due to infection; fissure or ulceration of the lateral nail groove, sometimes crusted with granulation-like tissue beneath the scab. The nail bed is most commonly involved. The commonest clinical signs are, in decreasing order, subungual hyperkeratosis (Fig. 21.52a–d), onycholysis, oozing (Fig. 21.53a–d), and nail plate destruction [259]. In particular, nail plate destruction is a discriminating feature with viral warts (Fig. 21.54a,b); the integrity of the nail is lost if the destructive malignant tumor infiltrates the nail matrix.

Subungual involvement was consistent in the 12 cases of Guitart et al. [274]. It may present with onycholysis and clipping away of the non-adherent portion of the nail plate shows hyperkeratosis or oozing ulceration of the nail bed. Longitudinal melanonychia is present in about 10% of subungual squamous cell carcinoma cases [286] (Fig. 21.55a,b), with classic pattern of the band [286–290] or irregular appearance [267, 291, 292].

![Figure 21.52](a–d) Bowen disease. Warty type.

![Figure 21.53](a–d) Bowen disease. Onycholysis and oozing type.
Bowen disease and squamous cell carcinoma of the nail unit may also present as onychopapilloma, fibrokeratoma (Fig. 21.56), as a potentially polydactylos process with the passage of time (Fig. 21.57), or onychomatricoma-like lesions (Fig. 21.58) [266, 293–295]. Longitudinal erythronychia was the main clinical presentation in two cases of subungual Bowen disease (Fig. 21.59) [165]. Localized pain may be noted, for example when the patient uses a keyboard.

**Evolution**

Bowen disease of the nail apparatus is a distinctive type of squamous cell carcinoma in situ that differs from other variants. It seems to evolve relatively often toward an invasive form. However, squamous cell carcinomas of the nail unit metastasize less often than other primary cutaneous squamous cell carcinomas. This relatively benign behavior results in a very good prognosis.

Figure 21.54 (a,b) Warty Bowen disease, with destruction of the plate. This is highly suspicious.

Figure 21.55 (a,b) Bowen disease associated with longitudinal melanonychia.

Figure 21.56 Bowen disease presenting as a fibrokeratoma. Courtesy of J. André.
Presence of ulceration, bleeding, or nodule formation indicates that the carcinoma has become invasive [296]. Bone involvement is seen in less than 20% of patients [3, 297]. Metastases have been reported in patients with hereditary ectodermal dysplasia [298, 299] and also in patients without ectodermal dysplasia [300–303].

**Differential diagnosis**
Diagnosis of Bowen disease and squamous cell carcinoma of the nail unit is often delayed or incorrect. Lesions mostly are present for several years before the correct diagnosis is made. The main differential diagnosis is a wart [259]. Other chronic inflammatory conditions, including bacterial infections [304], as well as pyogenic granuloma, subungual exostosis, onychopapilloma, onychomatricoma, malignant melanoma, glomus tumor, and subungual keratoacanthoma, and even acquired ungual fibrokeratoma may be evoked [284, 285].

**Diagnosis**
The key to diagnosis is the histological examination [261]. The diagnostic biopsy is often delayed because of the patient’s reluctance, technical difficulties, or because the physician has failed to suspect the disease. It should be noted, however, that an incisional biopsy specimen may only reveal an in situ carcinoma but examination of the whole residual lesion may show overt invasive or microinvasive clusters.

**Medical imaging**
Dermoscopy may be helpful to recognize Bowen disease [305]. The preoperative evaluation should include radiography to exclude osseous involvement because bony invasion is reported regularly in invasive squamous cell carcinoma [259].

**Pathology**
The histological picture is identical to that of Bowen disease of other skin areas [306]. The most important feature is the intact basement membrane. Some authors prefer to avoid the term Bowen disease for in situ squamous carcinoma occurring beneath the nail plate, because: (i) it is not always easy to separate invasive from in situ carcinoma; and (ii) it cannot be overemphasized that a biopsy specimen showing Bowen disease does not exclude the possibility of invasive carcinoma in other areas of the lesion [295, 296].

**Management**
The need for complete removal of the lesion cannot be overemphasized. However, even with sophisticated surgical techniques, recurrences are not uncommon, probably because HPV is difficult to eradicate [259]. Surgery is the preferred treatment for both Bowen disease and squamous cell carcinoma of the nail unit.
Considering the doubt one might have about the certainty a biopsy can offer in differentiating Bowen disease from invasive squamous cell carcinoma, one might prefer a treatment which is also effective against invasive squamous cell carcinoma [307]. The first-line surgical treatment of in situ or invasive squamous cell carcinoma of the nail unit can be a conventional surgical resection or Mohs micrographic surgery (Box 21.2). A perionychial squamous cell carcinoma without bone involvement requires complete removal with margins of 0.5–1 cm using conventional surgery. The value of Mohs micrographic surgery in invasive squamous cell carcinoma of the nail unit is a matter of debate. Some authors prefer this treatment to allow adequate excision with maximal preservation of normal tissue and function [259, 263, 296, 308–310], while others find high recurrence rates, up to 56% [261], likely caused by the difficult interpretation of horizontal sections on the nail unit and by the difficulty of preparing the specimen for cryosections. Surgery can be performed with routine instrumentation as well as with the CO₂ laser in a focused beam incisional mode, which avoids bleeding and ensures minimal postoperative discomfort for the patient. Excisional surgery may be used in some cases or for complete removal of the nail apparatus [261] with healing by secondary intention, grafting, or repair with a bridge flap [311]. Electrosurgery is a therapeutic alternative in a very few selected cases.

Non-surgical treatments with CO₂ laser, photodynamic therapy [312, 313], liquid nitrogen, imiquimod cream [314], or 5% 5-fluorouracil cream [259, 269, 315], with or without prior curettage and intraarterial infusion with methotrexate [316] have been used for treatment of Bowen disease of the nail unit but do not allow adequate histological control of tumor margins. Radiotherapy has been used in a case of multiple periungual Bowen disease and resulted in relapses and persistent anonychia [317]. The recurrence rate of all treatments taken together was reported to be 30.6% [259]. Amputation of the distal phalanx or more proximally is generally accepted to be first choice when there is bony or extensive soft tissue involvement, and also because radiation therapy has been associated with bone necrosis [47]. Fine needle aspiration cytology guided by ultrasound imaging may also be used to preoperatively evaluate lymph node involvement.

Verrucous carcinoma and carcinoma (epithelioma) cuniculatum (Figs 21.60, 21.61)

Verrucous carcinoma is a slow-growing, well-differentiated, rare squamous carcinoma variant. Carcinoma (epithelioma) cuniculatum is a term for an even rarer variant of verrucous carcinoma and is more often used as a misnomer.

**Box 21.2 Principles of management for nail unit squamous cell carcinoma**

- **First choice**: Mohs surgery
- **Second line**: conventional surgery with micrographic control of the margins on fixed tissue
- **Third line**: imiquimod cream, 5-fluorouracil cream with or without prior curettage, photodynamic therapy, and intraarterial infusion with methotrexate [316]
- **Fourth line**: amputation is mandatory only when there is bone involvement

---

**Figure 21.60** (a) Verrucous carcinoma. Courtesy of J. Van Geertruyden. (b) Verrucous carcinoma. Courtesy of S. Chiheb.
Verrucous carcinoma is a slow-growing but locally destructive, low-grade cancer of squamous cell origin with low or absent metastatic potential. It has been reported in several patients with nail involvement. Distalateral onycholysis and paronychia of the corresponding side were observed by McKee et al. [319] in a 38-year-old woman in whom the tumor had been present for at least 18 months. The second case started in an almost identical fashion. Progressively the inflammatory features were accompanied by subungual purulent material leading to disappearance of the nail plate. The nail bed was covered with multiple “holes” extruding toothpaste-like, foul-smelling, yellow-white material [320]. Matoso et al. [321] presented a patient illustrating the trap of many verrucous carcinomas: it is often misdiagnosed as a benign condition. Their patient had a 2-year history of a progressive right fourth fingernail verrucous plaque replacing and surrounding her entire fourth fingernail. Another patient had been treated by dye laser because the tumor was diagnosed as a subungual wart [322]. The patient of Coldiron et al. [323] presented with a verrucous growth of the distal portion of the thumb. It was a friable mass erupting from the pulp. A biopsy revealed that the entire pulp was involved down to the bone. A clinically similar verrucous and erosive tumor was found to originate from the nail bed of a great toe [324]. The great toe [325, 326] and fifth toe [327, 328] were involved with loss of the nail in three other patients. Verrucous carcinoma does not metastasize except in some cases in which the tumors were treated with radiation [329]. Subungual epithelioma cuniculatum was also seen in the racket thumb of a retired internist where the role of possible repeated radiation exposure cannot be excluded [333]. A possible verrucous carcinoma of the nail bed was also diagnosed in a psoriatic nail bed of a patient previously treated with methotrexate, UVB, and PUVA [331]. A role for HPV was suggested after identification of this virus in a recurrent carcinoma cuniculatum on a proximal nail fold [332]. Baran et al. [117] reported a 55-year-old woman with a periungual keratoacanthoma preceded by a wart and followed 6 months later by a papillomatous tumor involving two-thirds of the proximal nail fold associated with leukonychia caused by a verrucous carcinoma at the same site. The tumor was positive for oncogenic HPV 31 and 35. HPV-negative verrucous carcinomas have also been reported [321, 322].

The radiograph of most of the patients shows erosion or disappearance of the distal third of the phalanx but can also be normal in patients with extensive tumors [324]. Histopathologically, epithelioma (carcinoma) cuniculatum has a mounded (bossy) surface with the epidermis covered by a thin layer of keratin [318]. The epidermis is separated in foci by orifices, which act to drain narrow crypts “like rivers draining a marsh.” When cut in cross-section these crypts resemble tunnel openings “having the (cuniculate) structure of the burrows of a rabbit warren.” “Ordinary” verrucous carcinoma, whether of the foot or other sites, is markedly papillated and covered by a thick keratin layer. The keratin-lined invaginations extend deeply into a grossly hyperplastic (acanthotic) neoplastic epidermis and, when cut cross-sectionally, resemble keratin cysts. The neoplasm itself is composed of solid masses of typical keratinocytes with rounded, bulging, pushing, smooth bases and an intact basement membrane. Immunohistochemistry using antibodies to different cytokeratins, involucrin, and filaggrin as well as lectin histochemistry with peanut agglutinin only reflects the high degree of differentiation [333]. Filaggrin is present where keratohyalin can be seen in hematoxylin and eosin (H&E) stained sections and involucrin is also expressed by the majority of the tumor cells. Peptide nucleic acid (PNA) binding is variable with both completely positive and negative areas. Neuraminidase digestion unmasks the Friedreich–Thomsen antigen, thus rendering all tumor cells positive (E. Haneke, unpublished data). Differential diagnosis includes verrucae (even histologically) and keratoacanthoma which exhibits rapid growth and clinically aggressive behavior.

Epithelioma cuniculatum should not be confused with squamous cell carcinoma as it is verrucous and histologically shows little anaplasia. Pseudoepitheliomatous hyperplasia shows very irregular, jagged, papillomatous downgrowths when compared to epithelioma cuniculatum [323].

Radical resection with histologically confirmed tumor-free resection margins is the treatment of choice. Mohs surgery is an option because of its tissue-sparing capacity. Amputation is usually not necessary if there is no bone invasion. One case study suggests that intraarterial infusion chemotherapy with methotrexate is an effective...
method for treatment of subungual verrucous carcinoma with the advantage of preservation of morphology and function [334].

**Onycholemmal carcinoma** (Fig. 21.62)

Onycholemmal carcinoma is believed to be of onycholemmal origin and has a varied and often subtle presentation and indolent clinical course [335]. The tumor shows many similarities with malignant proliferating trichilemmal cyst and was hence termed malignant proliferating onycholemmal cyst [336] but nowadays it is known as onycholemmal carcinoma. However, Perrin et al. [337] proposed the term microcystic nail bed carcinoma for many of these onycholemmal carcinomas without sebaceous–apocrine differentiation. It is considered a distinct type of squamous cell carcinoma arising from the nail isthmus [338]. The first reported case was a 74-year-old woman with a subungual lesion of her right thumb that had slowly enlarged. Curettage led to rapid recurrence. The nail bed showed a warty tumor that eventually destroyed most of her nail and was surrounded by swollen, livid red tissue. Radiography showed considerable bone resorption. After biopsy, the distal phalanx was amputated. Histopathology showed a malignant tumor invading the nail bed, proximal and lateral nail folds, as well as the bone. In another case a 73-year-old woman presented with a cracked left thumb nail and nail dystrophy [339]. This gradual split was accompanied by pain, edema, and erythema in the ungual region. Clinical presentation may also be limited to partial onycholysis due to a small verrucous nodule under the nail plate [340] or extensive onycholysis with digital clubbing [337] and erosion of the nail bed [341]. Chaser et al. [338] reported six cases. Histologically, all cases showed a well-differentiated atypical infiltrative squamous proliferative lesion exhibiting a lobulated and cystic pattern of growth in the dermis. Abrupt keratinization reminiscent of trichilemmal keratinization was noted. Less aggressive digit-sparing treatment modalities, such as Mohs micrographic surgery and radiation therapy, are used as primary treatment modalities.

**Basal cell carcinoma**

Although basal cell carcinoma (BCC) is the most common malignant skin tumor, it is very rare in the subungual and periungual region. Only 28 patients and 29 cases of nail unit BCC have been reported since the first description by Eisenklam [342, 343]. Nail involvement was described in 18.3% of BCC of the dorsal hand [344], and in 95.7% of BCC in which a finger was involved. The lesion is usually present for many years before diagnosis. Most cases occur on the fingers [345], but lesions have also been reported on a fifth toe [346] (Fig. 21.63) and, more often, on the great toes [79, 347–350] that may develop into a large ulcerating mass [351]. BCCs are believed to originate from follicular structures; therefore, the decreased relative frequency of these structures in the nail unit may explain the low incidence of tumors at this location, despite a likely high amount of daily sun exposure. Also, the use of a UV nail lamp could not be linked to development of periungual BCC [352]. A link with trauma [345], azo pigments such as Solvent Red 8 [353], or nail polish [354] has been suggested in patients with periungual BCC.
The usual presentation is as a chronic paronychia or a periungual eczema, often associated with ulceration, granulation tissue, and pain [355–359]. The lesion may show a typical pearly, rolled border [360]. Erosion of the nail fold in combination with transverse ridging of the nail may mimic habit tic [361, 362]. Acquired longitudinal melanonychia in a white patient as the only manifestation of subungual BCC is unique [363].

The diagnosis can only be made by histological examination. Surgical excision is the treatment of choice, and Mohs micrographic surgery is often used in this delicate area [342, 354, 364].

Sweat gland carcinomas
Eccrine adenocarcinomas, or malignant sweat gland tumors, were traditionally divided into four types histologically [365]: eccrine porocarcinoma, syringoid eccrine carcinoma, mucinous eccrine carcinoma, and (clear cell) hidradenocarcinoma (also called clear cell eccrine carcinoma, malignant eccrine spiradenoma, or malignant eccrine acrosiroma). In 1984, Helwig [366] described an eccrine sweat gland carcinoma that appears to be different from these four types: (aggressive) digital papillary adenocarcinoma. Because most malignant neoplasms of the sweat glands are difficult to classify, alternative terms and diagnoses are still in use.

Periungual eccrine porocarcinoma (Fig. 21.64) is very rare and originates from cells of the eccrine duct epithelium. Requena et al. [252] reported a patient exposed to radiation for many years which resulted in chronic radiodermatitis of several digits on both hands. He displayed an ulcer in the lateral nail fold of the right third digit which extended into the nail bed. Histology was consistent with eccrine porocarcinoma. Other cases were described by van Gorp and van der Putte [367], Bhat et al. [368], and Ramirez et al. [369]. Moussallem et al. described a case mimicking onychomycosis [370]. All reported patients were over 65 years of age. The tumor has a high local recurrence rate and a tendency to lymphatic metastatic spread [368, 369].
Subungual syringoid eccrine carcinoma is extremely rare. A case of a 22-year-old woman presenting with this tumor under the nail of the hallux was presented by Grady et al. [371]. A mucinous adenocystic eccrine carcinoma was seen on the distal aspect of the right great toe of a 30-year-old black woman. The tumor was located just planar to the hyponychium, measuring approximately 15 mm in diameter. The lesion was freely mobile and tender. Histopathology showed multiple lobules of either solid, papillary, or trabecular tumor tissue with focally abundant mitoses [372].

Hidradenocarcinoma occasionally occurs in the ungual region. A 77-year-old African-American man presented with a 9-month history of a non-tender, enlarging nodule on the right third fingernail bed. The patient stated that the lesion began as a pigmented streak 1–2 years previously and had been rapidly increasing in size for a few months before presentation. Physical examination showed an ulcerated, red, dome-shaped nodule involving the right third finger proximal nail fold and the proximal three-quarters of the nail bed with destruction and loss of the overlying nail plate. The remaining few millimeters of attached nail plate on either side of the tumor showed hyperpigmentation. No axillary or epitrochlear lymphadenopathy was found. Excisional biopsy down to bone was performed and showed a multinodular tumor extending from the epidermis. The tumor comprised polygonal-shaped epithelial cells with distinctly demarcated cytoplasmic borders and pale to clear cytoplasm. These cells displayed pleomorphism, hyperchromasia, and nuclear atypia with numerous mitoses. Immunohistochemical stains revealed strong positivity with cytokeratin and rare scattered cells staining with S100 and carcinoembryonic antigen (CEA). A diagnosis of hidradenocarcinoma was made [373]. Another case of hidradenocarcinoma of the nail bed in a 76-year-old woman was reported by Son et al. [374]. She presented with a darkish discoloration that was gradually increasing in size. The nail had thickened and its contour showed a convex shape with mild tenderness. Initially, it was misdiagnosed as a fungal infection. A periungual case in a young woman was presented by Chang [375]. She presented with a small, round, tender, protruding lesion over the radial side of the right index fingertip of 3 months’ duration with a shallow ulceration. Biopsies had a benign aspect, and initially the lesion was misdiagnosed as pyogenic granuloma. A Mexican case presented as an impressive ulcerating but asymptomatic hidradenocarcinoma present for 5 years on the great toe of a 76-year-old man [376]. A case of hidradenocarcinoma of the tip of the right middle toe was reported by Jariwala et al. in 2010 [377]. Hidradenocarcinomas are rare and aggressive, with an approximate 50–75% rate of recurrence and the possibility of metastasis [378]. They may arise from long-standing benign eccrine spiradenoma or, less commonly, develop de novo [83]. The progression of benign eccrine spiradenoma to hidradenocarcinoma is slow with a lag of up to 20 years [379]. Surgery is the first-line treatment, consisting of wide excision ensuring negative margins. Mohs surgery might be indicated.

(Aggressive) digital papillary adenocarcinoma (ADPA) is a rare eccrine sweat gland tumor that was described by Helwig in 1984 [366]. In 1987 the first case series of 57 cases was published [380]. Currently, the literature reports a total of 129 cases of ADPA, of which 104 tumors presented in the hand [381]. The tumors were originally classified as adenoma and as adenocarcinoma but the original view of a benign ADPA did not predict biological behavior since several “benign” adenomas showed metastasis during follow-up. The neoplasm occurs as a single, pink, slowly enlarging painless rubbery nodule, almost exclusively on the fingers, toes, and adjacent skin of the palms and soles. Uncommonly, the tumor can present with tenderness, a central keratotic plug, ulceration, and bleeding [382]. Clinically, ADPA should be considered in the differential diagnosis along with calluses, knuckle pads, cysts (ganglion, inclusion, mucous), giant cell tumors, pyogenic or foreign body granulomas, hemangiomas, gout, squamous cell carcinoma, infections, and metastatic lesions [382, 383]. Males are much more often affected than females (7 : 1), and the average age of presentation is between 43 and 52 years [380, 384]. Three cases were observed in patients under the age of 20 years. Microscopic features [382, 383, 385] are distinct from other eccrine sweat gland tumors and often lead to the diagnosis of metastatic carcinoma such as that of the breast. The characteristic histological features included tubuloalveolar and ductal structures with areas of papillary projections protruding into cystic lumina. The stroma varied from thin, fibrous septa to areas of dense, hyalinized collagen. The histological features can be quite bland with little cytological atypia. ADPA was formerly thought to be solely eccrine as it is typically located in areas devoid of apocrine glands. However, a case of an ADPA characterized by areas of sebaceous differentiation has been reported, supporting apocrine differentiation in at least some instances [383]. Duke et al. [386] reported a local recurrence rate of 28% and a regional and distant metastasis rate of 14% in a series of 64 patients. Because of its tendency to recur locally, wide local excision should be performed as definitive initial treatment. Sentinel lymph node evaluation should be considered for high-risk tumors where lymph node spread is a concern [381].

Sebaceous gland carcinoma
Kasdan et al. [198] reported on a 46-year-old man with a 6-month history of increasing swelling of the radial aspect of the distal phalanx of his right index finger. The swelling was neither painful nor tender. Radiographs did
not reveal bone abnormalities and the presumptive diagnosis was epidermoid cyst. At operation, a grayish-white irregular mass was fixed to the skin, well circumscribed, and pseudoencapsulated. It was composed of markedly malignant cells of epithelial origin, organized in irregularly shaped islands with areas of focal necrosis. The cells exhibited a somewhat lobular pattern, with many mitotic nuclei showing hyperchromatism and pleomorphism. The cytoplasm was eosinophilic with vacuolation, suggesting sebaceous gland origin. The pathological diagnosis was poorly differentiated sebaceous carcinoma. A formal ray amputation of the finger was carried out.

**Soft tissue tumors**

**Benign fibrous tumors**

There are many different types of fibroma that may develop in the subungual and periungual area. They may represent separate entities or be variants of the same pathology. These fibrous tumors comprise a large variety of clinical types ranging from fibrous dermatofibroma to digital fibrokeratoma. This contrasts markedly with the uniformity of the histology of some fibrous tumors. This is an argument for a continuum of a single pathological process including Koenen tumor, acquired fibrokeratoma, and dermatofibroma of the nail apparatus, though the location of the origin of the fibroblastic proliferation could offer a clue to the diagnosis [387]. For all these reasons fibrokeratoma is described with the other fibrous tumors.

**Koenen tumors**

**Definition**

Koenen periungual fibromas develop in about 50% of cases of tuberous sclerosis (epiloia or Bourneville–Pringle disease) which is a dominantly inherited multisystem disease affecting the central nervous system, eyes, skin, cutaneous appendages, kidneys, heart, blood vessels, and bones. Koenen tumors (≥2) are one of the major diagnostic criteria of tuberous sclerosis complex.

**Etiology**

Two major gene loci have been identified where mutations can cause the tuberous sclerosis complex with apparently indistinguishable phenotypes: TSC1 at 9q34, and TSC2 at 16p13.3 [388].

Rarely are Koenen tumors the only evidence of tuberous sclerosis [389–391]. A 40-year-old man with familial retinoblastoma was seen to have typical multiple periungual fibrokeratomas without any other evidence of tuberous sclerosis. A germinal mutation of one allele of the RB gene (tumor suppressor gene) was found; since in some cases of tuberous sclerosis a mutation of the tuberin gene, also a tumor suppressor gene, was demonstrated, the authors speculated that multiple periungual fibromas might indicate an anomaly of tumor suppressor genes [392]. Longitudinal erythronychia was associated with a subungual nodular tumor in the nail area.

**Clinical features**

The periungual fibromas usually appear between the ages of 12 and 14 years and increase progressively in size and number with age. In children up to 18 years of age the reported incidence is 15% but fibromas are completely absent under the age of 2 [393].

Koenen tumors appear as mostly asymptomatic, firm, smooth, skin-colored or reddish papules around or under fingernails and toenails. Periungual fibromas are more common than subungual fibromas [394], and they can be found more frequently on toes than on fingers. Individual tumors are small, firm, round, flesh-colored or reddish, mostly asymptomatic, with a smooth surface (Fig. 21.65a,b). The tip of the tumor may be slightly hyperkeratotic, resembling fibrokeratoma. They grow out of the nail fold, eventually overgrowing the nail bed and destroying the nail plate. Depending on their location,
they may cause longitudinal depressions in the nail plate. They sometimes also grow in the nail plate similar to a dissecting fibrokeratoma or onychomatricoma [395]. Even a tiny hyperkeratotic lesion in the cuticle area may produce identical longitudinal nail grooves and have the same significance as Koenen tumors [396] (Fig. 21.66). However, a single ungual fibrokeratoma is apparently not a sign of a minor expression of tuberous sclerosis [397]. Excessively large tumors are often painful and should be excised at their base. Bone cysts may occur in tuberous sclerosis although those in the distal phalanx are excessively rare [398] and have to be differentiated from a number of other osseous lesions causing cystic defects in the distal phalanx (see “Aneurysmal bone cyst (arteriovenous fistula)”)

Pathology
Histologically, no difference has been found between isolated ungual fibrokeratoma and Koenen tumors [397]. In Koenen tumors, two portions can be distinguished [399]: a small distal segment with loose collagen and many blood vessels, and a larger proximal part built up of dense collagen bundles and fewer capillaries. Neither neural or glial appearance [400] nor arteriovenous anastomoses [401] could be found. Ma et al. [402] reviewed histological features of Koenen tumor in 18 tuberous sclerosis complex patients. Depending on the relative proportions of vascular proliferations and stromal fibrosis they identified three subtypes: an angiomatous subtype, a fibrotic subtype, and a mixed subtype.

It thus appears that the Koenen tumor can be considered as a particular type of fibrokeratoma which can be subdivided according to its clinical appearance, its location, and its origin into the following groups:

- Fibrokeratomas originating from the dermal connective tissue. These are posttraumatic or appear spontaneously and are usually located on the fingers (acquired digital fibrokeratoma).
- Fibrokeratomas originating from the proximal nail fold or the surrounding connective tissue. They are located in the nail fold and can be hereditary (tuberous sclerosis) or acquired (for example, garlic clove fibroma).

Treatment
The indication for treatment is often pressure-induced pain or cosmetic reasons. Malignant transformation has not been reported. Surgical excision from its very base is the treatment of choice in most patients. Tumors growing out from beneath the proximal nail fold are removed after reflecting the proximal nail fold back by making lateral incisions down each margin in the axis of the lateral nail grooves. Subungual fibromas are removed after avulsion of the corresponding part of the nail plate. Electrodesiccation, CO2 laser vaporization, tangential excision, and phenolization have been described [403, 404]. Recently, Muzic et al. reported successful treatment of Koenen tumors with topical rapamycin under occlusion [405]. Recurrences are common in tuberous sclerosis patients, because they are prone to develop these tumors.

Acquired ungual fibrokeratoma (acquired digital fibrokeratoma, garlic clove fibroma)

Definition
Acquired ungual fibrokeratoma is a benign tumor of fibrous tissue probably identical to acquired digital fibrokeratoma [406] (Fig. 21.67) and garlic clove fibroma [407, 408] (Fig. 21.68).
**Etiology**

Trauma and, in some cases, infection [409, 410] are thought to be major factors initiating acquired periungual fibrokeratoma. Also use of ciclosporin has been attributed to development of acquired digital fibrokeratoma [411] but clinically these tumors differed greatly from typical digital fibrokeratoma. No reactivity with HPV immunostaining was found in digital fibrokeratoma [412].

**Clinical features**

They are acquired, benign, spontaneously developing, asymptomatic nodules with a hyperkeratotic tip and a narrow base which occur mostly in the periungual area, under the proximal nail fold (Fig. 21.69a), in the lateral folds (Fig. 21.69b), rarely on the bed (Fig. 21.69c), or even originate in the matrix. Most ungual fibrokeratomas emerge from the most proximal part of the nail sulcus, growing on the nail and causing a sharp longitudinal depression [413] (Fig. 21.70). Some of these lesions originate from within the matrix and thus grow in the nail plate to eventually emerge in the middle of the nail (Fig. 21.71a–c); these intraungual fibrokeratomas are also called “dissecting ungual fibrokeratoma” because they divide the nail plate [395]. Subungual fibrokeratomas arise from the nail bed [414] or from an exostosis [415, 416]. Dermoscopy shows numerous dark red, clumped structures surrounded by white keratotic septa [417]. These meshwork-like septa may correspond to the histologically retracted hyperkeratotic epidermis.

Fibrokeratomas may have two, three, or even more tips (Fig. 21.72) and reach a considerable size (Fig. 21.73) [418–421]. A giant fibrokeratoma of the nail bed was described by Hashiro et al. [422]. Takino and Mitoh [423] reported a case in which the lesion was located beneath the nail and visible under the free margin of the great toenail.

Ungual or periungual fibromas are one of the major diagnostic criteria of the tuberous sclerosis complex [424].

**Medical imaging**

Magnetic resonance imaging accurately depicts the component emerging from the proximal nail fold in the split...
of the nail plate. Overall, MR images highlight the deep implantation close to the nail root. The signal of the tumor depends on the histological type: very low signal on all sequences for the dense and numerous collagen bundle type; high signal on T2-weighted images in cases where there is mucoid stroma. Intralesional septa and the acanthotic epidermal coverage show regular limits and a signal identical to that of normal epidermis. MRI is also able to depict a tumor involving the ventral aspect of the proximal nail fold with an epithelial invagination.

**Differential diagnosis**
This includes fibroma, keloid, Koenen tumor, recurring digital fibrous tumors of childhood, dermatofibrosarcoma, fibrosarcoma, cutaneous horn, eccrine poroma, pyogenic granuloma, verruca vulgaris, and exostosis [425]. Cases of Bowen disease [284], aggressive digital papillary adenocarcinoma [426], and squamous cell carcinoma [263] masquerading as acquired digital fibrokeratoma have been described. Pseudofibrokeratoma should be considered as a clue for Bowen disease [285].

**Pathology**
Histological examination of 50 cases of acquired digital fibrokeratoma [424] disclosed three histological variants of these lesions:

- a tumor composed of thick, dense, and closely packed collagen bundles (Fig. 21.74)
- a variant with an increased number of fibroblasts in the dermis (Fig. 21.75)
- a type with an edematous and poorly cellular structure (Fig. 21.76).

The acquired digital fibrokeratoma is considered to result from new collagen formation by fibroblasts. The acanthosis of the epidermis is probably secondary to the
dermal alteration. Immunohistochemistry shows that the fibroblasts are vimentin positive and many of them stain with HHF 35, a monoclonal antibody said to be specific for muscle actin. Thus the cells may be myofibroblasts.

Management
Surgical treatment is the same as for Koenen tumors and will depend on the size and location of the fibroma. Usually the tumor is incised around its base and dissected from the bone. Superficial removal usually results in recurrence.

Invaginated fibrokeratoma [427]
Three cases of a variant of fibrokeratoma involving the ventral aspect of the proximal nail fold have been observed. They have three characteristic features.

- Proximal to the normal matrix, and in the same axis, there is epithelial invagination.
- The floor of this infolding acts as an accessory matrix, without a granular layer, and gives rise to a “pseudonail” made of keratin, similar to the normal nail plate.
- This accessory nail apparatus, lying on a dermal fibrous nodule, is sharply demarcated from the surrounding dermis, having a large base which narrows at the tip, giving the typical appearance of an incipient fibrokeratoma of type I in Kint and Baran’s classification [399].

Subungual filamentous tumor
Subungual filamentous tumors are thread-like horny subungual lesions growing with the nail plate and emerging from under the free edge (Fig. 21.77). They are visible through the nail plate as a whitish, yellowish to brown streak of approximately 1 mm width, sometimes containing some clotted blood, but they are always wider than splinter hemorrages. They may cause a longitudinal rim or a distal split in the nail. The diagnosis is confirmed by looking under the free edge of the nail plate where they appear as a horny pearl which can be scraped off when cleaning the hyponychial space and pared down painlessly when the nail is cut. It was thought that this entity might be a narrow, extremely hyperkeratotic fibrokeratoma; however, in contrast to ungual fibrokeratoma, it never grows wider than 1–1.5 mm, is always located under the nail, and lacks a fibrotic core. It has therefore to be considered as another entity.

Figure 21.74 Acquired periungual fibrokeratoma (type I).

Figure 21.75 Acquired periungual fibrokeratoma (type II).

Figure 21.76 Acquired periungual fibrokeratoma (type III).

Figure 21.77 Subungual filamentous tumor.
Differential diagnosis includes onychopapilloma and subungual warty papilloma (Table 21.4).

Radical treatment requires nail bed exposure and excision of the base of the lesion. Histology shows a subungual rim of keratinous substance in an irregular whorled arrangement. The nail bed may show a single, slightly papillomatous projection with marked hypergranulosis.

Fibrous dermatofibromas/histiocytomas or “true” fibromas
Dermatofibromas of the ungual area are extremely rare. One study among 5000 cases showed that 26 (0.5%) dermatofibromas arose on a digit [428]. Four of these were on a distal phalanx but none involved the nail unit. Kinoshita et al. [429] reported a case of dermatofibroma involving the matrix and noted bulging and thinning of the thumbnail plate. Moon et al. [430] presented a case of myxoid dermatofibroma as a slowly enlarging subungual mass on the right great toe. Examination revealed a firm, round hyperkeratotic mass of 15 mm in diameter, which distorted the whole nail plate.

Two cases of “unguioblastic fibroma” on the right middle finger of a 30-year-old man and the right thumb of a 45-year-old woman have been described [431]. The tumors were 1.5 and 2.4 cm in diameter, respectively, and involved the proximal nail fold. The lesions showed peripheral bands of benign-appearing, basaloid epithelium forming a reticulated pattern of internal growth. Squamous differentiation mainly occurred where the epithelial retinacula merged. Mild papillomatous change was seen in some areas. The stroma was fibrocellular with a collagenous matrix and cells arranged in a parallel array. Mast cells were frequent. Stroma cells were positive for factor XIIIa and CD 34; squamoid epithelial cells stained for AE1–AE3. We have seen two cases of matrix fibroma clinically producing transverse overcurvature. Histopathology showed a dense cellular stroma made up of very fine collagen fibers and thus resembling the stroma of onychomatricoma [432].

Fibromas usually develop as painless, slow-growing nodular tumors. They may be spherical or oval in shape, and firm or elastic in consistency. They can develop in any dermal structure of the nail apparatus and may be mobile or fixed [433].

Fibromas may become cherry shaped or polypoid and lift the nail in the distal area (Fig. 21.78). In addition to deformity of the nail, displacement of the finger pulp and erosion of the distal phalanx may lead to unnecessary amputation. The tumor is smooth on the dorsal aspect of the proximal fold, or on the nail bed. It is usually spherical, resembling a small pea, or alternatively may be ovoid (Fig. 21.79). On the lateral nail fold the fibroma may also be spherical but without the collar of slightly elevated skin seen in acquired periungual fibrokeratoma. Fibroma of the matrix results in nail dystrophy [429] (Fig. 21.80). Therefore, clinical features vary according to the anatomical site, ranging from simple thinning of the nail plate to a longitudinal canal, which

<table>
<thead>
<tr>
<th>Features</th>
<th>Ungual fibrokeratoma</th>
<th>Subungual filamentous tumor</th>
</tr>
</thead>
<tbody>
<tr>
<td>Growth of lesion</td>
<td>Slow, insidious</td>
<td>Only keratin filament</td>
</tr>
<tr>
<td>Location</td>
<td>On, in, or under nail</td>
<td>Always under nail plate</td>
</tr>
<tr>
<td>Differential diagnosis</td>
<td>Koenen tumor, fibroma, wart, Bowen disease</td>
<td>Onychopapilloma of the nail bed</td>
</tr>
</tbody>
</table>

Table 21.4 Differential diagnostic features of fibrokeratoma and subungual filamentous tumor.
is sometimes partially covered by nail keratin to form a tunnel-like structure.

Lebouc [434] described a plexiform fibroma of the nail bed which had developed after severe trauma. Heller [435] described a sub- and periungual fibroma the size of a pigeon's egg.

Histological features are a dermal hypocellular reticular nodule, composed of very dense connective tissue bundles with elastic fibers present with ill-defined demarcation, and are similar in all our patients in spite of clinical variation [387]. Factor XIIIa was negative in the core of the tumors but in one case the papillary dermis above the tumor showed a slight increase of factor XIIIa cells surrounding the vessels.

Two types of dermatofibroma histology are classically described [436]: fibroma (or fibrous dermatofibroma) (Fig. 21.81a,b), and histiocytoma. In the latter, uncommon

Figure 21.80  (a) Fibroma of the matrix resulting in nail dystrophy. (b) Fibroma at operation.

Figure 21.81  (a) Fibroma nail dystrophy. (b) Fibroma at operation showing the matrix location of the tumor. (c) Dermal fibroma, histopathology, same patient. (d) Storiform collagenoma. Courtesy of A. Tosti.
in the nail apparatus, histiocytic proliferation is sometimes associated with an angiomatous component, most often referred to as sclerosing hemangioma. Rupp et al. [437] reported a unique case with darkening of the right great toenail, slight edema, moderate erythema, and thickening of the nail, which proved to be a tumor mass within the distal phalanx. Focal erosion of the dorsal cortex with extension of the mass into the lower dermis was present. This was, histologically, a benign fibrous histiocytoma clinically mimicking a melanoma. Reed and Elmer [438], in a review of 28 cases of solitary acral fibrous tumors, distinguished three histological varieties: acquired digital fibrokeratoma (ADFK); irritation fibroma; and fibroma molle. This classification is difficult to apply in the cases we have studied and should be discarded. Several authors [439, 440] have assimilated periungual fibroma and periungual fibrokeratoma as interchangeable terms and have not used Reed's classification.

Several connective tissue tumors are easily ruled out (Box 21.3).

Three main histological clues distinguish isolated “true” fibroma from ADFK and from other tumors of the nail apparatus:

- the lesions are composed of areas of very thick, hypocellular, hyalinized collagen bundles, in a haphazard array
- there is an ill-defined nodule situated mostly in the reticular dermis
- the elastic fibers are most often absent or scarce.

Radiographs may depict erosion of bone and thickening of the soft tissues. There are no calcifications. MRI findings are suggestive with a mainly low signal nodule on all sequences and very dark irregular areas of extremely dense connective bundles (Fig. 21.82). These patterns and the lack of an obvious peripheral rim differentiate them from acquired fibrokeratomas. Faint and heterogeneous uptake of contrast media may be noted.

**Box 21.3 Differential diagnosis of ungual true fibroma with other fibrous tumors of the nail apparatus**

<table>
<thead>
<tr>
<th>Sclerotic fibroma [443, 449, 450]</th>
<th>Leiomyoma [452, 453]</th>
</tr>
</thead>
<tbody>
<tr>
<td>Well circumscribed</td>
<td>Muscle stains red with Masson trichome (by contrast, fibroma stains blue)</td>
</tr>
<tr>
<td>Overlying epidermis thin</td>
<td>Each muscle cell has its own periodic acid–Schiff (PAS)-positive basal membrane</td>
</tr>
<tr>
<td>Collagen bundle in a “whorl-like” pattern</td>
<td>Leiomyoma is labeled by smooth muscle actin and desmin [436]</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Fibroma of tendon sheath</th>
<th>Recurrent infantile digital fibroma</th>
</tr>
</thead>
<tbody>
<tr>
<td>Well circumscribed</td>
<td>First year of life</td>
</tr>
<tr>
<td>Attachment to tendon or tendon sheath</td>
<td>Characteristic inclusion bodies visualized with phosphotungstic acid hematoxylin stain [436]</td>
</tr>
<tr>
<td>Gradual transition between cellular and more hyalinized areas</td>
<td></td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Pleomorphic fibroma</th>
<th>Rudimentary supernumerary digit</th>
</tr>
</thead>
<tbody>
<tr>
<td>Multinucleated cells with large hyperchromatic nuclei</td>
<td>Present at birth</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Keloid [436, 451]</th>
<th>Dermatomyofibroma [444, 448]</th>
</tr>
</thead>
<tbody>
<tr>
<td>Well circumscribed</td>
<td>Uncommon cutaneous neoplasm of myofibroblastic origin</td>
</tr>
<tr>
<td>Papillary dermis normal</td>
<td></td>
</tr>
<tr>
<td>Hypocellular areas admixed with more cellular areas</td>
<td></td>
</tr>
</tbody>
</table>
A case of “osteoid fibroma” of the tip of the right little finger in a 10-year-old girl was described by Stein [441]. Subungual myxoid fibromatous fibroma was seen in a 54-year-old man who had a 1-year history of a painless, slowly growing mass subungually in his right thumb. The nail was thickened with subungual hyperkeratosis and paronychia. Histopathology showed a hypocellular neoplasm with haphazard arrangement of thick collagen separated by myxoid stroma and dilated blood vessels. Among ordinary appearing fibroblasts were atypical cells with large pleomorphic and hyperchromatic nuclei, as well as multinucleated cells, some of which exhibited a rosette arrangement. The cytoplasm was pale pink and scant. The cells were positive for vimentin, and many atypical large cells reacted strongly with anti-CD34 [442].

Tosti et al. [443] described a case of storiform collagénoma (Fig. 21.81), known as sclerotic fibroma [444] and presenting as a 1 cm subungual nodule associated with onycholysis of the first left finger. This peculiar benign fibromatous tumor typically occurs in patients with Cowden disease, which was not found in Tosti et al.’s case. The subungual fibrotic nodule reported by Sigel [445] in a case of Cowden disease was not explored histologically.

Calcifying aponeurotic fibroma (CAF) is a rare benign soft tissue tumor that primarily occurs on the distal portion of the extremities of children and adolescents. Schonauer et al. [446] reported a 44-year-old male with a 2-year history of an enlarging, painful, slightly hyperkeratotic nodule of the tip of his right index finger in the subungual area. Plain radiographs revealed a nodular mass with foci of calcification and bone erosion. Histology revealed the presence of proliferative fibroblasts with the absence of cytological atypia and mitotic figures in a myxoid stroma rich in calcification and concentric lamellar bone. Osteoclast-like cells were also present. Radiological studies showed no bone involvement.

Recently, Plaza et al. [447] proposed the term “acquired reactive digital fibroma” for the benign fibroblastic tumor they diagnosed in five patients with a mean age of 61 years. All tumors showed a striking predilection for the subungual or periungual region. Approximately 2–6 weeks after an injury, patients noticed a growing mass in the digits, either the thumb or the great toe. Physical examination showed a non-tender, well-delineated, immobile nodular mass on the distal portion of the digit. One patient had an overlying ulcer. Histologically, all cases were composed of short fascicles of benign-appearing fibroblastic spindle cells with vascularized and somewhat myxoid stroma. There were no mitotic figures in the lesion.

Dermatomyofibroma is an uncommon cutaneous neoplasm of myofibroblastic origin. Prior clinical reports of dermatomyofibroma show a predilection for the shoulder, axillae, or upper arm. Cheng and Nydorf [444] have described a case of solitary dermatomyofibroma on the right fifth finger at the proximal nail fold that is thought to be the first reported case occurring at this location. The patient was a 58-year-old woman with an asymptomatic, slowly enlarging nodule. Pathology revealed interweaving fascicles of bland, uniform spindle cells within the reticular dermis. Adnexal structures were preserved within the lesion. The spindled cells demonstrated immunoreactivity for vimentin, muscle-specific actin, and smooth muscle actin, consistent with a myofibroblastic origin. Together, these pathological findings are those of a dermatomyofibroma. Another patient presented with a long-standing poorly defined tumor on the proximal nail fold, firm and scar-like in consistency [448].

**Chondromyxoid fibroma**

Chondromyxoid fibroma is an extremely rare benign but locally aggressive bone tumor [454]. It presents in the second to third decade and is most often found around the knee. The clinical presentation is usually chronic pain (85%) and/or swelling (65%). Few cases of chondromyxoid fibroma in the nail region have been reported. Kim et al. [455] reported a 53-year-old woman with a slow-growing, painful tumor of the great toe of the left foot which she had first noticed 25 years ago. The tumor was relatively well demarcated, gray-tan in color, and solid. A long delay of 10 years was also noticed in the 22-year-old man presenting with a painless lump on the terminal phalanx of the left fourth toe [456]. Radiological findings were a trabecular pattern, cortical thinning, and cortical erosion. He underwent a primary toe amputation. Bill Chang and Hing Lui [457] report a 40-year-old woman who developed a gradually enlarging swelling on her right great toe after a minor contusion 7 years before. Clinically, there was a mildly tender, bony hard mass over the distal part of her right great toe. Radiographs showed an expansile lesion with a sclerotic border affecting the base of the distal phalanx. There was cortical erosion and calcification. MRI showed a T1 hypointense and T2 heterogeneous mildly hyperintense mass in the midportion of the distal phalanx of her right great toe. The diagnosis was made histologically after amputation.

Histology differentiates these lesions from chondroblasticoma and chondrosarcoma. Chondromyxoid fibromas have highly variable histological patterns [455]. Typically, they are characterized by hypocellular chondromyxoid lobules surrounded by dense peripheral bands or condensations of fibroid elements. Rarely, variously sized foci of osteoclast-like giant cells; degenerative changes such as foamy macrophages and cholesterol clefts; osteoid and/or woven bone production; and giant nuclei of tumor cells are described. Treatment options include simple curettage with or without bone grafting, en bloc excision, and primary amputation. Adjuvants such as
intralesional polymethyl methacrylate are recommended after limited surgery [454]. Malignant transformation and a recurrence rate after therapy, mostly curettage, of 15–20% have been reported.

**Keloid**

Hypertrophic scars and keloids result from injuries to the nail fold or nail bed, but are rare in this location. They present as relatively large, smooth, firm nodules [458] (Fig. 21.83). Keloid formation of the fingers is particularly noticed after syndactyly release surgery, and might be associated with macrodactyly and Proteus syndrome [459–461]. Almost all of these patients were white, in contrast to the usual keloid patients who are preferentially from African ancestry. Keloid formation on the great toe after chronic paronychia secondary to ingrown nail has been reported but is very rare [462]. Digital keloid has also been reported in patients with aggressive ingrowth of conjunctiva over the cornea [463]. This ocular pterygium–digital keloid dysplasia syndrome likely follows an autosomal dominant pattern of inheritance. Large keloids were seen after electrosurgical resection of the hallux and second toenails because of recurrent ingrown nails in a 25-year-old man (E. Haneke, unpublished data). Keloid exhibits hyalinized collagen bundles; the fibroblasts are contiguous with, and parallel to, the thick collagen bundles which are separated from the epidermis by nearly normal papillary dermis. Additionally, keloids are well circumscribed and elastic fibers are not present.

Treatment of keloids is problematic. Standard treatment (pressure, topical or intralesional corticosteroids, and re-excision) was unsuccessful in resolving periungual keloids. Adjunctive methotrexate treatment was successful in several patients [459, 460]. Surgical excision with a skin graft and intralesional corticosteroid injection was effective in a 4-year-old boy [461]. The keloid recurred on the edge of the skin graft and was treated with intralesional steroids. A compression cuff applied for 24 hours per day for 3 years was shown to be effective in a patient with keloid on the small toe [464].

**Knuckle pads**

Knuckle pads are asymptomatic, discrete, round, soft and freely movable, keratotic, nodular papules and plaques which may indicate the presence of another underlying or concomitant disorder. They rarely interfere with normal nail growth. Mostly they are skin-colored but hyperpigmentation or hypopigmentation has also been observed. The dorsal surface of the proximal interphalangeal joints is most frequently involved (Fig. 21.84), but they have also been noted on the distal interphalangeal joints and metacarpophalangeal joints, and may occasionally occur on the thumbs and toes. Commonly they appear between 15 and 30 years of age and persist through adulthood. The diagnosis can be made on the clinical picture, and biopsy of suspected lesions may only be considered to exclude conditions with similar appearing morphology [465]. Histology shows hyperkeratosis and an increase in the thickness of collagen bundles [466].

Primary knuckle pads are benign lesions unassociated with other cutaneous disorders and generally do not require treatment. Knuckle pads secondary to repeated trauma are called pseudo-knuckle pads [467], or “chewing pads” in children. Knuckle pads may also be associated with fibrosing conditions such as Dupuytren contractures, Ledderhose disease, and Peyronie disease, and genetic disorders such as epidermolytic palmoplantar keratoderma and Bart–Pumphrey syndrome. Severe knuckle pads in children have been attributed to a mutation in the GJB2 gene in families with knuckle pads, palmoplantar

![Figure 21.83](image1.png)  
(a) Keloid of the nail bed. (b) Keloid following grafting of the nail bed. Courtesy of S. Goettmann-Bonvallot.  

![Figure 21.84](image2.png)  
Figure 21.84 Knuckle pads.
keratoderma, and sensorineural hearing loss [468]. In particular, knuckle pads of the feet should be a signal for an association with an inherited syndrome.

**Infantile digital fibromatosis (recurring digital fibrous tumors of childhood, benign juvenile digital fibromatosis, inclusion body fibromatosis)** [469]

**Definition**

Infantile digital fibromatosis is an uncommon benign proliferation of fibroblastic and myofibroblastic cells that typically occurs in the dermal tissue of the digits of young children [470].

**Clinical features**

Infantile digital fibromas are round, smooth, domeshaped, non-tender, shiny, firm to tense dermal nodules, typically less than 2 cm in diameter, on the lateral side of the digits with a smooth flesh-colored surface reddish or livid red in color, similar to keloid (Fig. 21.85a) [471–473]. Characteristically, the thumbs and great toes are spared. The lesions may become clinically evident within the first year of age, and in up to one-third of cases immediately after the birth. There are also rare descriptions of this disease in older children, adolescents, and adults [474, 475]. The lesion has also been described after syndactyly release [473], and in association with digitocutaneous dysplasia [476]. Fingers are more often affected than toes. On reaching the nail unit, the lesions may elevate the nail plate, leading to dystrophy but not to destruction. They may cause considerable distortion of the digits. Often the tumor is multicentric, occurring on several digits.

Ryman and Bale [477] reported 30 cases, seen over 36 years: 20 females and 10 males. Fingers and toes were equally affected. Multiple lesions occurred in 50% of patients, more often in the fingers, especially on adjacent fingers. Two patients had bilateral lesions. Dabney et al. [478] and Piñol-Aguadé et al. [479] observed firm planter nodules in one of their three cases with infantile digital fibromatosis.

Location and age are very suggestive for the diagnosis of infantile digital fibromatosis, but histology is often required to confirm the diagnosis [473].

**Differential diagnosis**

Differential diagnosis includes pseudoinfantile digital fibromatosis with hypertrophic lateral lips of the great toe in early infancy (see Chapter 5, Fig. 5.2a), fibrosarcoma, and neurofibrosarcoma. Digitocutaneous dysplasia, also known as terminal osseous dysplasia with pigmentedary defects, is a rare X-linked, male lethal, dominant genetic syndrome. Nail abnormalities in patients with this syndrome include digital fibromas [476, 480]. These digital fibromas appear to be only histologically distinct from those that occur in patients with infantile digital fibromatosis. Cerebriform connective tissue nevus [481] (Fig. 21.86) and the multiple, soft, dome-shaped tumors present in a patient with systemic sclerosis but histologically reminiscent of cutaneous focal mucinosis [482]...
should also be ruled out. Progressive thickening of the soles of the feet was accompanied in a 10-year-old girl by fleshy, cerebriform elevations over the plantar surfaces with extension onto the sides and dorsal aspect of several toes. The most striking biochemical abnormality was the marked reduction in the production of collagenase. Similar patients have been reported [483] also suffering from multiple hamartomas including linear epidermal nevi.

Pathology
Histologically (Fig. 21.85b), in about 2% of the fibroblasts, paranuclear inclusion bodies 3–10 μm in diameter can be seen in properly fixed specimens using stains such as iron hematoxylin, methyl green–pyronin, and phosphotungstic acid–hematoxylin [484]. They are also visible in hematoxylin and eosin stained sections as globules slightly smaller than erythrocytes [485]. Zina et al. [486] studied two cases of infantile digital fibromatosis by electron microscopy and immunohistochemistry, using rabbit anti-actin sera. The tumor cells were typical myofibroblasts, containing inclusion bodies and bundles of microfilaments. Immunohistochemistry has shown that the paranuclear inclusions consist of vimentin and actin filaments. Currently it is thought that their presence most likely represents a deviation in the complex process of myofilament assembly in myofibroblasts and smooth muscle cells. Histopathologically, infantile digital fibromatosis may be confused with dermatofibroma, fibroma, and scar tissue.

Management
The benign character of the lesions combined with spontaneous resolution [487, 488], the high recurrence rate, and complications after surgical excision has led to a much more conservative approach when lesions are asymptomatic [470]. Many will use a watch and wait method, but others have advocated for some type of injection that may speed along the regression process, including corticosteroids or intralesional fluorouracil.

Cryosurgery may accelerate the natural involution. However, lesions may cause functional impairment thereby warranting therapeutic intervention [489]. Options include excision and skin grafting, Mohs micrographic resection, and injection of chemotherapeutics. Surgery necessitates going down to the fascia and tendon to avoid recurrence, and thus can be mutilating. Amputations sometimes performed in the past (38 of 115 cases of Ryman et al.) can no longer be justified [477]. The recurrence rate can be as high as 60% following tumor excision, which is reflected in the name “recurring digital fibrous tumors of childhood.”

Juvenile hyaline fibromatosis syndrome
Juvenile hyaline fibromatosis syndrome (JHF) is an autosomal recessive condition which was termed juvenile hyaline fibromatosis II by Kitano et al. [490] to describe the condition previously reported as molluscum fibrosum, mesenchymal dysplasia (Puretic syndrome), systemic hyalinosis, and fibromatosis. About 40 cases of this syndrome with abnormal growth of hyalinized fibrous tissue have been described in the world literature. It is characterized by skin lesions, muscle weakness, and flexion contractures of large joints. The skin lesions are multiple, large, subcutaneous, painless, hyaline tumors, or small, pink, or pearly papules with a translucent appearance and gelatinous consistency. They are found in the head and neck region, on the trunk, and at the tip of the digits where acroosteolysis may be seen. Occurrence of digital nodules has been described as the first sign of JHF in some patients [491]. Excessively large periungual hyaline fibromas were reported (Fig. 21.87) [492, 493]. Distal osteolysis with destruction of the distal phalanx causes nail deformity [494, 495] whereas no nail changes were described despite excessively large periungual hyaline fibromas in the case of Rimbaud et al. [496] redescribed by Schaller et al. [493].

The tumors exhibit a reduction of normal collagen and fibroblasts and show lake-like deposits of a hyaline substance. “Chondroid” cells are seen in this eosinophilic substance. Electron microscopy showed the fibroblasts to contain a markedly dilated rough endoplasmic reticulum and Golgi apparatus filled with granular and fibrillar material [493, 497]. Excision of cutaneous lesions is almost always followed by local recurrences [498].

Malignant fibrous tumors
Dermatofibrosarcoma protuberans
Dermatofibrosarcoma protuberans (DFSP) is a rare, malignant soft tissue neoplasm which is often misdiagnosed due to its indolent clinical course. Most DFSPs are located on the trunk. Expression near the nail unit is extremely rare. A pink, firm, multilobulated and painful mass involved the palmar aspect of the distal thumb of a 31-year-old black woman. The fibrous growth of rubbery consistency was well circumscribed and surrounded by normal skin [499]. A 55-year-old Japanese woman presented with a dark-brownish hyperkeratotic plaque on the dorsum of her right first toe proximal to the posterior nail fold. The initial clinical diagnosis of wart prompted treatment with cryotherapy. After that, a glossy milky-white tumor appeared [500]. Pigmented pachyonychia of the second toe was the clinical presentation of a subungual tumor in a 55-year-old Caucasian woman (Fig. 21.88a). Histology revealed the characteristic histology of DFSP [501] (Fig. 21.88b).

Surgery is the treatment of choice for DFSP. Mohs micrographic surgery and partial amputation have been used in a 62-year-old woman with recurrent DFSP of the left hallux [502]. This avoided a metatarsophalangeal amputation that might have interfered with ambulation.
Hemangiomas of infancy are the most common soft tissue tumor in children. However, hemangiomas of the nail bed and tip of the digit are extremely rare. They exhibit the classic course with fast growth in neonates and slow spontaneous involution which begins by 12–18 months (Fig. 21.89). These hemangiomas are not at risk of becoming large masses with tissue damage and compression [503]. In three babies, aged 2–9 months, reported by Piraccini et al. [503] hemangioma produced pseudoclubbing caused by capillary vessel proliferation in the soft tissue of the subungual region, which was associated with a purple-reddish discoloration of the nail that typically faded with compression. In one child, the hemangioma was deeper, producing also drumstick enlargement of the distal digit. The nail matrix was only uplifted and was not damaged by the vascular tumor, so the nail plate remained completely normal.

Capillary malformations (port wine stains and telangiectases)
Capillary malformations, port wine stains, or nevus flammeus are the most common congenital vascular malformations. These developmental defects are present from birth, frequently occur on the extremities, and are usually permanent. They may look violet through the nail (Fig. 21.90). Paradoxically, when the color of the angioma is pronounced, true leukonychia can be observed (Fig. 21.91) [504].

Angioma
Subungual angiomas often present as painful swellings with focal blue-red discoloration, mostly beneath the lunula.
Venous and arteriovenous malformations

Venous malformations of the nail apparatus alone are rare and should be left untreated unless they show rapid growth, impair the function of the hand, or cause tissue destruction.

The shape of the nail may remain normal but the nail bed is blue in cases of small lesions [504] (Fig. 21.92). It may blacken if thrombosed. Venous malformations may arise in the bone or soft tissue (Fig. 21.93). When primary in the bone, they have a characteristic radiological appearance of linear striations parallel to the shaft of the bone. Soft tissue venous malformations are more common lesions and may be radiographically manifest as local soft tissue masses, phleboliths in the soft tissue, and pressure erosion of the underlying bone [505].

Histopathology shows ectatic capillary or venous channels with normal-looking endothelial cells. MRI easily shows the vascular patterns of the malformation but is not able to differentiate it from other vascular tumors. Images may be misleading without the injection
flow void artifacts, signal hemorrhage, and high enhancement after injection of gadolinium must be sought. MRI also assesses the extension of the lesion into the soft tissues and the relations with the digital collateral vessels (Fig. 21.94). These relations may be better highlighted with angio-MRI sequences. The original location, soft tissues or bone, is easily depicted on MR images.

Growing and massive venous malformations involving a finger have been reported occasionally [506, 507]. One was reported in a young boy with a congenital vascular malformation involving the left thumb, first web space, and index finger, which rapidly enlarged during his first year of life to envelop the entire left thumb, first web space, and radial aspect of the index finger [506]. It completely impaired the function of his left hand. He could not pinch or grip because of the bulk of the mass and could not lift his arm because of the weight of the hand. Because the malformation totally impaired the function of his hand and because of the failure of injection sclerotherapy, he had radical resection of the venous malformation at 42 months of age. Gu and Jeong [507] reported a 15-year-old girl who acquired a vascular malformation at the age of 12. She presented with a slightly enlarging soft mass involving the pulp, distal phalanx, and nail bed on her left third finger. It caused an unpleasant pinprick feeling with intermittent pain and a nail bed gradually turning blue, and she felt mild discomfort in fine prehension. Radical excision including partial distal phalanx and nail bed was performed to achieve complete removal.

Heller’s case with “angioelephantiasis” probably represented Klippel–Trénaunay syndrome (i.e. a capillary and venous complex combined malformation), or Parkes–Weber syndrome (i.e. a limb overgrowth syndrome due to arteriovenous fistula). The bed of the thumb was dark blue and four toenails were reduced to keratotic plugs [458].

Acquired digital and subungual arteriovenous malformations are exceptionally rare, with only 15 published cases [508]. Similar vascular lesions have been described over the years under a variety of names such as cirsoid aneurysms, arteriovenous hemangiomas, periungual and subungual arteriovenous tumors, and acral arteriovenous tumors [508, 509]. The digit and the nail bed have a purple hue with progressive resorption of the distal phalanx and shrinking of the nail plate presenting a slight transverse overcurvature (Fig. 21.95). Arteriovenous malformation is usually congenital but an acquired type is also known, of which most are due to injury. A firm, bluish, non-pulsatile vascular nodule has been reported
in the lateral nail fold of the left little finger [509]. Kadono et al. [510] described six cases of acquired lesions that presented as reddish to purple macules located on the distal phalanx of young adults with history of preceding trauma in some cases. None was located subungually. Clinically the lesions consisted of collections of reddish dots. The color faded on diascopy and returned immediately after decompression. Histologically, dilated venous and arterial vessels were present in the dermis. Most patients with subungual arteriovenous malformations present with painful localized longitudinal erythronychia, distal nail plate fissuring, nail fragility, and splinter hemorrhages [508]. One case had a bluish lunula and another had a reddish lesion beneath the nail plate. Another patient presented with an erythematous swelling of the proximal nail fold associated with a localized nail dystrophy distally from this lesion [511]. A 36-year-old woman presented with a 2-year history of an asymptomatic localized longitudinal erythronychia of her left thumbnail [508]. The streak had developed during her second trimester of pregnancy and had been stable for the past 2 years. The longitudinal specimen was excised, starting at the distal matrix and extending through the nail bed to the hyponychium. Histopathology showed features of an arteriovenous malformation with both thick- and thin-walled benign-appearing vascular channels. Pseudo-Kaposi syndrome can be seen (Fig. 21.96) [504]. The diagnosis is easily made by Doppler ultrasound evaluation and digital arteriography.

**Angiokeratoma circumscriptum and solitary angiokeratoma**

Angiokeratoma circumscriptum presents as a hyperkeratotic plaque containing warty red-blue papules and nodules. These angiokeratomas are often present at birth. Dolph et al. [512] described a 12-year-old girl with a raised, firm, bluish-purple nodule over the dorsal aspect of the distal index finger. It enlarged with the concomitant appearance of several black dots at the periphery. Histology showed a typical angiokeratoma. Hasegawa and Tamura [513] reported a 74-year-old man with suspected diagnosis of subungual melanoma. He presented with acquired longitudinal melanonychia (Fig. 21.97a) of his left fourth toenail which had been present for 10 years but had increased in depth of color in the past months. Dermoscopy showed a streak composed of red-brown to dark brown globules and dots with a light brown background, suggestive of a hemorrhage (Fig. 21.97b). Based on histopathological features (Fig. 21.97c), the lesion was diagnosed as a subungual solitary angiokeratoma.

**Aneurysmal bone cyst (arteriovenous fistula)**

Aneurysmal bone cysts (ABCs) may occur in the distal phalanx of young people. They are benign, osteolytic, expansive, and hemorrhagic bone lesions, usually encountered in children and adolescents. The lesion has
been named aneurysmal bone cyst because the contour of the affected bone suggests a blow-out type of distension which resembles the saccular protrusion of the walls of an aneurysm and also because cystic blood-filled spaces are encountered at surgery. The nature and histogenesis are still unclear; it is classified as an indeterminate tumor of intermediate malignancy, locally aggressive. ABCs show characteristic translocations in 70%; the rest are secondary, without a translocation, and occur in reaction to other, usually benign, bone lesions. Solitary bone cyst of the distal phalanx is exceptional and may belong to the group of ABCs. Goldsmith [514] reported a clubbed nail deformity overlying a bulbous distal end of the left second toe which was tender. Radiography revealed an expanded distal phalanx with an ultra-thinned cortex and cyst-like loss of substance in the main body of bone.

ABCs may develop in all bones of the skeleton but ABCs arising in the distal phalanx of the hand occur only occasionally [515–519]. They are revealed by pain, and sometimes by swelling and nail clubbing over a relatively short duration of weeks to months.

X-ray and MRI are the radiological examinations of choice [520]. On radiographs, the phalanx may be excessively enlarged and almost completely occupied by osteolytic tissue, simulating a malignant tumor [196] (Fig. 21.98). Computed tomographic scans of ABCs reveal fluid levels [521] but they are a non-specific finding [522]. MRI may be evocative of ABC with intraosseous cystic blood-filled spaces with horizontal levels [523]. However, these findings are not pathognomonic.

Biopsy is essential for diagnosing ABC and to rule out telangiectatic osteosarcoma and unicameral bone cysts.

The natural course is resolution, spontaneously or within 4–6 weeks after simple biopsy. In other cases, the cyst may become aggressive, entirely destroying one end of the bone, raising fears of malignancy [520]. Real malignant transformation occurs only in cases of irradiation. If spontaneous resolution does not occur, intralesional sclerotherapy with alcohol is an effective treatment option [520]. Curettage has also been described, particularly if the hand is involved [524]. Surgical resection or amputation of a digit guarantees against local recurrence but at the cost of reconstruction problems and of possible complications that the benign nature of ABC cannot justify.

Subungual keratosis with longitudinal erythronychia (see “Onychopapilloma of the nail bed”)

This lesion was first described as “acquired subungual superficial capillary malformation.”

Intravascular papillary endothelial hyperplasia (pseudoangiosarcoma of Masson)

This rare reactive lesion usually occurs in dilated thrombosed veins. The pure form is an intravascular papillary endothelial hyperplasia without a preexisting lesion. It is usually a small (usually less than 2 cm), painful mass in the subcutaneous tissue [525]. It commonly occurs in a digit, and almost all intravascular papillary endothelial hyperplasias in the digits are of this type. Kitagawa et al. [525] presented five patients with intravascular papillary endothelial hyperplasia; all were found in the digits. Blue discoloration of the skin was found in all lesions, and a presumptive preoperative diagnosis of venous malformation had been made for four of the lesions. A 50-year-old male hairdresser was observed who presented with a slightly tender, swollen, bluish-red tip of his right index finger suspicious of a metastasis to the terminal phalanx. The nail plate appeared enlarged and the radial nail wall had almost disappeared. The patient did not remember a specific traumatic event although repeated microtrauma was possible. Radiography did not reveal bony changes. An incision was made along

Figure 21.98 (a) Aneurysmal bone cyst: histiocytic, fibroblastic, and multinucleate cells. (b) Aneurysmal bone cyst. Courtesy of J.L. Schmutz.
the lateral aspect of the terminal phalanx and a dark-blue, segmented lesion became visible which upon further dissection turned out to be vascular.

In general, MRI is able to differentiate between venous malformations and intravascular papillary endothelial hyperplasia [525, 526].

Histopathological examination reveals intravascular papillary endothelial hyperplasia in a thrombotic, thin-walled, very ectatic vein [306].

The lesion is essentially cured by simple excision. Successful treatment by the beta-adrenergic antagonist nebivolol has also been reported [527].

Epithelioid hemangioma and epithelioid hemangioendothelioma

Epithelioid hemangioma, previously designated angio-lymphoid hyperplasia with eosinophilia (ALHE), histiocytoid hemangioma, or pseudopyogenic granuloma, is a benign vascular tumor mostly occurring in the skin and subcutis of middle-aged women. In contrast, epithelioid hemangioendothelioma is a malignant tumor with high morbidity and mortality; it is therefore classified as a fully malignant neoplasm and no longer seen as intermediate between a hemangioma and a conventional angiosarcoma. Similar neoplasms occur in other sites such as the lung, liver, and bone. Because of its rarity, epithelioid hemangioma may be misdiagnosed as a metastatic carcinoma or other neoplasm [528].

Avenel et al. [529] described a 40-year-old woman with angiomatous nodules affecting the fingertip, lateral nail folds, and nail bed (Fig. 21.99a). The histological and ultrastructural changes were consistent with the diagnosis of epithelioid hemangioma [530–532]. Dannaker et al. [533] reported a case with simultaneous cutaneous and bone involvement of epithelioid hemangioma. The patient, a 31-year-old Mexican-American man, presented with nail changes including onycholysis of the distal area, longitudinal splitting, subungual and periungual erythema, and paronychial swelling with purulent drainage. Biopsy specimens showed a proliferation of histiocytoid endothelial cells with intracytoplasmic vacuoles and associated vascular lumen formation. Radiation therapy resulted in significant clinical improvement.

Tosti et al. [534] observed a 47-year-old man with liver cirrhosis due to hepatitis C who had noted multiple painless lesions of the right middle finger and fingernail for 2 months. Apart from several 1–3 mm large angiomatous papules, he had a 5 mm large vegetating nodule that destroyed the nail plate and was bright red, smooth, and superficially eroded. Biopsy revealed inflammatory cells, nests and cords of endothelial cells, and abnormal vessels lined by large endothelial cells that had vesicular nuclei and prominent nucleoli. Small lumina were present within endothelial cell aggregates, and other lumina were formed by confluent cytoplasmic vacuoles (Fig. 21.99b).

The endothelial cells were positive for factor VIII and vimentin. Epithelioid hemangioma masquerading as paronychia was described in a 42-year-old female who had a 6-month history of progressive swelling and some tenderness of the left great toe. The toe was diffusely swollen, the pulp was bluish-red, and there was increased curvature of the nail of the left great toe. On radiography, a large lytic lesion of the distal phalanx was shown without any reactive new bone formation and with expansion of the proximal end of the phalanx and an associated large soft tissue mass. The typical multicentric morphology was recognized, on the basis of bone isotope scan. Histopathology of curetted tissue showed numerous vessels of varying size and development, many with large epithelioid endothelial cells. The associated inflammatory infiltrate contained foci of eosinophils [535]. Risitano et al. [536] described a 23-year-old man with epithelioid hemangioma of the nail bed of his left ring finger, and Imbing et al. [537] reported on a 26-year-old black woman with slightly blue-black subungual discoloration in the right small fingernail together with more lesions on the palm. An irregular but well-circumscribed
slightly painful brown-red nodule of approximately 10 mm in diameter found on the tip and nail bed of the third toe of a 69-year-old Japanese woman was accompanied by osteolysis of this toe [538]. The lesion had developed slowly during the previous 2 months. The 32-year-old patient presented by Conill et al. [539] also had osteolytic bone lesions. Ward et al. [540] observed a 39-year-old man with a tender multinodular swelling of the left middle fingernail causing nail deformity and splitting. Histology shows a benign vascular proliferation associated with a dense lymphocytic infiltrate with many eosinophils. The capillaries are lined with plump endothelial cells protruding into the lumen. Pachydermoperiostosis was associated with epithelioid hemangioma involving the face and the palms in a patient of Kanekura et al. [541].

Complete surgical excision is the primary therapeutic approach to epithelioid hemangioma. Other therapies that have been reported to have some effect include radiotherapy, corticosteroid injections, photodynamic therapy, corticosteroid therapy, ultralong-pulsed dye laser, CO2 laser, argon laser, oral indometacin, imiquimod, tacrolimus ointment, and cryotherapy [542–544].

Multifocal epithelioid hemangioendothelioma is a highly malignant neoplasm. Occurrence on or near the nail unit has been reported only once. It was diagnosed on the sole of the foot and tip of the toes in a 63-year-old female patient. The diagnosis was confirmed by the demonstration of the endothelial markers factor VIII, CD 31, and CD 34. MRI and digital subtraction angiography showed multifocal bone involvement. Treatment with interferon alfa led to partial regression [545].

Acral angioosteoma cutis

Acral angioosteoma cutis is a benign lesion of unknown pathogenesis [546]. In 2006, Googe et al. [547] described in an abstract 11 patients with a benign vascular and bony proliferating lesion occurring on the acral skin and designated it as “acral angioosteoma cutis.” It is clinically characterized by an exophytic lesion resembling pyogenic granuloma on the acral skin, such as the first toe, heel, finger, thumb, bottom of the foot, and palm, combined with histological findings of multiple tiny spicules composed of woven bone between well-formed capillaries proliferating in the superficial dermis. Three more patients have been described in detail since then [546, 548, 549]. Song et al. [546] reported a 58-year-old woman with an asymptomatic, flesh-colored, exophytic tumor 1 cm in diameter and with a glossy, ulcerated surface, located subungually on the third toe of the left foot. The lesion lifted the nail plate and had developed suddenly 2 months earlier without a definite history of trauma at the site. Another case was that of a 43-year-old female who presented with an ulcerative, dome-shaped subungual nodule on the left fourth toe, which appeared to be a pyogenic granuloma [548]. It developed after the toe bumped into a rock 18 months previously. Biopsy findings were compatible with acral angioosteoma cutis and incompatible with calcifications in pyogenic granuloma, based on the absence of a lobular capillary proliferation. The lesion was excised with electrocauterization and did not recur. A third case was reported in a 12-year-old girl who presented with a solitary, tender, crusted nodule on her left great toe [549]. She had been suffering from an ingrown nail and the lesion had first appeared 2 months earlier after a partial nail extraction. Physical examination revealed an erythematous to blackish, somewhat firm, crusted periungual nodule, measuring 5 mm in diameter, with paronychia on her left great toe. The lesion was removed by curettage and did not recur. Histology confirmed the diagnosis as acral angioosteoma cutis. A recurrent subungual angioosteoma in a pregnant woman was described and was cured after deeper removal and vigorous electrodesiccation [550].

Acral pseudolymphomatous angiokeratoma of children (APACHE)

Acral pseudolymphomatous angiokeratoma of children, known as APACHE, is a rare, benign, cutaneous pseudolymphomatous disorder of unknown etiology. Ramsay et al. [551] described five children (four girls, one boy) who developed a unilateral eruption of multiple (up to 40) angiomatous papules on the extremities (in four patients on the feet and in one patient on the hand), between the ages of 2 and 13 years. The lesions were red-violaceous, discrete, irregularly shaped papules 1–4 mm in size with a hyperkeratotic collar occurring over acral sites (Fig. 21.100). The provisional diagnosis in three of the

Figure 21.100 APACHE syndrome. Courtesy of L. Dahl.
patients was angiokeratoma of Mibelli, but the lesions were more numerous and chilblains were not a feature. The lesions persisted, with some decrease in size, during follow-up periods of up to 16 years. Kaddu et al. [552] reported a 16-year-old boy who had several deep-red, scaly papules and nodules on his left first and fifth toes with small papules also on the lateral nail wall. Linear arrangement of cutaneous lesions in APACHE in association with nail dystrophy was reported by McFaddin et al. [553] on the left index finger of a 10-year-old girl. Lesions were pseudovesicular in appearance with prominent dystrophy of the adjacent central nail plate. The lesions can be asymptomatic or they may be painful and may tend to bleed. When located in the nail region, longitudinal nail splitting, nail deformity, or onycholysis may be present [554–556]. Clinically, the lesion is similar to an angiokeratoma, whereas histologically it corresponds to a distinct type of pseudolymphoma [554]. Immunohistochemistry is required to distinguish APACHE from cutaneous lymphoma [557]. Histological findings consist of hyperkeratosis, slight thinning of the overlying epidermis with elongated rete ridges at the margins, and a well-circumscribed dense nodular lymphocytic infiltrate present throughout the dermis, extending from the subcutis to the dermoepidermal junction, but without involving the epidermis. There is an equal number of B- and T-cells and the T-suppressor cells (CD8) outnumber helper T-cells (CD4) [554]. In one patient the lesions were destroyed by curettage and did not recur.

Hara et al. [555] reported on a 14-year-old Japanese girl presenting with multiple lesions in a linear fashion on just one finger with involvement of the medial aspect of the nail as partial onycholysis. The histology corresponded to that of a pseudolymphoma but there was a lack of prominent thickened capillaries. There were epidermal changes including liquefaction degeneration of the basal cells with predominance of CD4 lymphocytes at the upper portion of the infiltrate and CD8 at the lower one.

The elective therapeutic choice is total excision of lesions. Intralesional corticosteroid therapy, cryotherapy, and radiotherapy are also described but recurrences are frequent [557].

**Pyogenic granuloma (granuloma telangiectaticum, botryomycoma)**

**Definition**

Pyogenic granuloma is a benign eruptive hemangioma. There is a lot of confusion in the literature between real pyogenic granuloma and granulation tissue. The latter is mostly induced by anticancer therapies.

**Etiology**

Minor penetrating skin injury is the best-known provoking factor for pyogenic granuloma. Many other factors have been reported as inducers of this tumor [558]: drugs (retinoids, antiretrovirals, antineoplastic drugs) (Table 21.5), peripheral nerve injury including Guillain–Barré syndrome [558, 559], retronychia [558], friction [558, 560], inflammatory systemic diseases (cutaneous sarcoidosis, psoriasis, and seronegative spondyloarthritis) [558], accompanied by onychomadesis following cast immobilization [561–563]. However, considering the clinical appearance and histopathology, many of these “pyogenic granulomas” should have been called granulation tissue. Extensive granulation tissue due to an ingrowing toenail may mimic a periungual pyogenic granuloma, and it has also been observed in patients treated with aromatic retinoids [564] as well as with indinavir [565] and ciclosporin [566]. The pyogenic granuloma-like lesions occurring after cast immobilization are histologically different and are discussed in the section “Coccal nail fold angiomatosis.”

**Clinical features**

The lesion starts around the nail as a minute red papule which rapidly grows to the size of a pea or even a cherry. Tenderness and a ready tendency to bleed are

<table>
<thead>
<tr>
<th>Drug</th>
<th>Reference</th>
</tr>
</thead>
<tbody>
<tr>
<td>Acitretin</td>
<td>[558]</td>
</tr>
<tr>
<td>Capecitabine</td>
<td>[558, 589–591]</td>
</tr>
<tr>
<td>Cetuximab</td>
<td>[558]</td>
</tr>
<tr>
<td>Ciclosporin</td>
<td>[566]</td>
</tr>
<tr>
<td>Docetaxel</td>
<td>[558, 592]</td>
</tr>
<tr>
<td>Etaercept</td>
<td>[593]</td>
</tr>
<tr>
<td>Etoposide</td>
<td>[558]</td>
</tr>
<tr>
<td>Etretinate</td>
<td>[594, 595]</td>
</tr>
<tr>
<td>5-Fluorouracil (systemic)</td>
<td>[596]</td>
</tr>
<tr>
<td>Gefitinib</td>
<td>[558, 597–599]</td>
</tr>
<tr>
<td>Imatinib</td>
<td>[600]</td>
</tr>
<tr>
<td>Indinavir</td>
<td>[558, 565, 601, 602]</td>
</tr>
<tr>
<td>Isotretinoin</td>
<td>[594, 603, 604]</td>
</tr>
<tr>
<td>Lamivudine</td>
<td>[558, 601, 602]</td>
</tr>
<tr>
<td>Levothryroxine</td>
<td>[605]</td>
</tr>
<tr>
<td>Mitoxantrone</td>
<td>[606]</td>
</tr>
<tr>
<td>Paclitaxel</td>
<td>[607]</td>
</tr>
<tr>
<td>Rituximab</td>
<td>[608]</td>
</tr>
<tr>
<td>Sirolimus</td>
<td>[609]</td>
</tr>
<tr>
<td>Tazarotene (topical)</td>
<td>[610, 611]</td>
</tr>
<tr>
<td>Tretinoin (topical)</td>
<td>[612]</td>
</tr>
<tr>
<td>Zidovudine</td>
<td>[558, 601]</td>
</tr>
</tbody>
</table>
characteristic features. With time, its surface may become eroded by necrosis of the overlying epidermis. Crusting may mimic a malignant melanoma. A typical collarette runs around the base of the lesion.

Pyogenic granuloma is commonly located at the proximal nail fold (Fig. 21.101) but may develop distally in the hyponychium region with onycholysis (Fig. 21.102), in the nail bed, or even in the matrix after a penetrating wound of the nail plate. Prolonged frictional trauma may result in pyogenic granuloma in the toenail bed (Fig. 21.103a,b) [560].

**Differential diagnosis**

Histopathological confirmation of the diagnosis is mandatory since many cases of delayed diagnosis of melanoma of the nail unit are due to this frequent confusion [567–569]. Also squamous cell carcinoma [570], basal cell carcinoma [571], angioosteoma cutis [549], cavernous angioma, pseudopyogenic granuloma, hemangiosarcoma, and Kaposi sarcoma of the nail unit [572] may be confused clinically with pyogenic granuloma. Moreover, dermoscopic features, such as the rail sign observed in pyogenic granuloma, are not specific enough to make a definitive accurate diagnosis [573].

**Pathology**

Histological investigation of the specimen is essential to rule out amelanotic melanoma and squamous-cell carcinoma (Fig. 21.53c).

**Management**

Therapy should be as simple as possible to avoid disfiguring scars or nail deformity. Pyogenic granuloma may be removed by excision at its base [574] followed by electrodesiccation or application of Monsel’s or aluminum chloride solution. The use of argon, CO₂, and 585 nm flash-lamp pumped pulsed-dye lasers is also curative [575–578].

---

**Figure 21.101** Pyogenic granuloma following an epidermal break on the proximal fold.

**Figure 21.102** Pyogenic granuloma developed distally.

(a) (b)

**Figure 21.103** (a) Pyogenic granuloma of the nail bed resulting from frictional trauma: (a) before, (b) after partial avulsion.
Also, intralesional triamcinolone acetonide injections [579], sclerotherapy [580], phenolization [581, 582], and microembolization may be considered. Topical therapy with imiquimod 5% cream may be effective [583, 584] but produces a marked inflammatory response with severe discomfort. Topical timolol was an effective and mild therapy for pyogenic granuloma on the distal phalanx [585, 586], and may also be considered in children, especially when other treatment modalities are challenging or could result in significant scarring [587]. Propranolol 1% cream was also shown to be very effective in ten patients, including three patients who continued their chemotherapy with an unmodified dose [588].

**Coccal nail fold angiomatosis**

A peculiar case of reactive vascular lesions growing out from under several nail folds was observed in a girl after her hand had been splinted for a wrist trauma. They were erosive, slightly oozing, asymptomatic tumors. The affected nails showed pronounced Beau's lines. Histopathology was reminiscent of, but not identical to, pyogenic granuloma with considerable vessel proliferation in an edematous tissue rich in lymphocytes and plasma cells. Streptococci were grown in culture. Treatment with antibiotics led to complete cure [613]. Three patients have been seen with coccal nail fold angiomatosis, all after trauma of the hand or wrist [306]. Two identical cases were seen by Tosti et al., who speculated that this might be a peculiar type of sympathetic reflex dystrophy [563]. It is likely that cases described as Beau’s lines and pyogenic granulomas following hand trauma and cast immobilization were identical [561–563, 614].

**Lymphangioma circumscriptum**

Lymphangioma circumscriptum or superficial lymphatic malformation is the most common lymphangioma. It occurs in infancy or early childhood but the distal digit is an extremely unusual site. Clinically, the lesion generally presents as a cluster of small, cutaneous, translucent vesicles, which resemble frog spawn (Fig. 21.104). Some of the vesicles can be filled with fresh or altered blood [615]. Histopathology shows endothelium-lined spaces, which may be so closely applied to the lower surface of the epidermis that they may simulate intraepidermal vesicles. They are in communication with large subcutaneous cisterns consisting of muscle-coated lymphatic vessels. Therefore, excision has to be wide and deep [451]. Combined radiofrequency current and 900 nm diode laser [616] and sodium tetradecyl sulfate sclerotherapy [617] have also been used with some success.

**Glomus tumor**

**Definition**

Glomus tumors are benign vascular hamartomas containing all the neuromyoarterial cells of the normal glomus apparatus in the reticular dermis. The vast majority of glomus tumors are located in the subungual region, most likely because of the high concentration of glomus bodies at this site. The glomus tumor was first described by Wood [618] as a painful subcutaneous “tubercle.”

**Epidemiology**

Seventy-five percent of glomus tumors occur in the hand, especially in the fingertips and particularly the subungual area. One to 2% of all hand tumors are glomus tumors [619]. The age of the patients at the time of diagnosis ranges from 30 to 50 years [620] but pediatric cases have also been reported [621, 622]. Men are much less frequently affected than women.

**Clinical features**

Pain is the predominant symptom. It is intense, often pulsating, or may be spontaneous or provoked by the slightest trauma. Changes in temperature, especially from warm to cold, may trigger pain radiating up to the shoulder. Sometimes the pain is worse at night. In one case it was reported that even polishing the nail was unbearable [623].
There are two main clinical presentations:

1) A small reddish or bluish spot of several millimeters (<1 cm) in diameter seen through the nail plate (Fig. 21.105a,b). An erythematous focus that does not blanch totally with pressure and is associated with sharp pain probably represents a glomus tumor. Often it is visible in the lunula.

2) A longitudinal erythronychia with distal notching or overlying longitudinal fissure (Fig. 21.106a,b).

One-half of the tumors cause minor nail deformities, ridging and fissuring being the most common. Subungual hyperkeratosis with onycholysis is rare [624]. Intraosseous location is unusual [625, 626]. Enlargement of the thickened nail and of the purple soft tissues with moderate pain of the fourth right finger was present for 20 years in a 95-year-old woman [627]. A painless nodular growth emerging from beneath the proximal nail fold of the left fourth toe of a 61-year-old man is a unique presentation. At surgery, the stalk was followed down to its base and was seen to arise from the nail matrix [628].

Typical subungual glomus tumors are frequently reported in patients with von Recklinghausen neurofibromatosis type 1 [629]. One case was reported to occur concomitantly with an onychomatricoma [630].

Malignant glomus tumors (glomangiosarcomas) are rare and are generally found in the lungs as tumors of over 4 cm in size [631]. Only one case of glomangiosarcoma on the radial aspect of the volar skin over the distal joint of the thumb has been described [632]. Several cases were described as malignant angiosarcomas or colloid sarcomas until Barré and Masson [633] published their investigations on two glomus tumors.

**Exploration**

Love [634] reported that localization of the tenderness to an area the size of a pinhead was suggestive of glomus tumor. For a positive Love’s pin test, the patient should experience severe pain and reduction in pain when the skin overlying the tumor is pressed with a pinhead, ballpoint pen, end of a paperclip, or Kirschner wire (Fig. 21.106b); this allows the tumor to be exactly located for surgery (Fig. 21.106c).

Glomus tumors may be tested for by placing an ice cube on the nail to exacerbate the pain (cold test). A tourniquet placed at the base of the digit stops the pain; also a blood pressure cuff inflated to 300 mmHg

---

**Figure 21.105** (a) Glomus tumor in the nail bed presenting as a blue spot. (b) Glomus tumor in submatrical location visible through the lunula.

**Figure 21.106** (a) Glomus tumor presenting as a painful longitudinal erythronychia with distal onycholysis and notching. (b) Love test allows precise location of the tumor for surgery (c).
before or immediately after minor trauma abolishes the pain response (Hildreth test) [635].

According to Bhaskaranand and Navadgi’s series, the Love test is 100% sensitive and shows an accuracy of 78% [636]. The cold sensitivity and Hildreth test have sensitivities of 100% and 71%, respectively, and specificities of 100%.

**Differential diagnosis**

This includes all causes of nail pain such as subungual warts, keratoacanthoma, subungual exostoses, enchondroma, and leiomyoma, but also inflammatory processes like paronychia, osteitis, and subungual whitlow. The most common misdiagnoses are neuroma, causalgia, gout, and arthritis. These have resulted in disastrous therapeutic attempts such as posterior rhizotomy and amputation [619]. Exceptionally, a glomus tumor might be totally painless. Patients have been wrongly referred to psychiatrists due to misdiagnosed glomus tumor where no nail alteration was visible.

**Diagnosis**

Diagnosis is usually based on the presence of the characteristic classic triad of severe pain, pinpoint tenderness, and cold sensitivity.

**Medical imaging**

Probing and transillumination may help to localize the tumor if it is not clearly visible through the nail [634, 635].

A slight rise in surface temperature can be detected by thermography; dynamic telethermography shows the lesion about three times its actual size [637].

Dermoscopy can help to preoperatively localize the tumor (see Chapter 4, Figs 4.40 and 4.71).

Plain radiography may reveal a depression on the dorsal aspect of the distal phalangeal bone or even a cyst in about 50% of cases [638, 639].

If the tumor cannot be localized clinically, by dermoscopy [640], on radiography, or using ultrasound, MRI may be preferable as it offers the highest sensitivity and a better assessment of the extent of the lesion. High-resolution MRI (see Chapter 6) is able to depict normal glomus bodies with T2-weighted images and after injection of gadolinium (Fig. 21.107). Three main findings are well highlighted by MRI: the signal, the location, and the limits of the tumor. The enhancement is very high after injection of gadolinium and the signal is also elevated on T2-weighted images (Fig. 21.108). Thin three-dimensional (3D) contiguous gradient echo slices are the most appropriate to depict a slight erosion of the dorsal aspect of the distal phalanx (Fig. 21.109). The coexistence of several tumors may be diagnosed (Fig. 21.110).

**Pathology**

Histology shows a highly differentiated, organoid tumor. It consists of an afferent arteriole and vascular channels lined with endothelium and surrounded by irregularly arranged cuboidal cells with round, dark nuclei and pale cytoplasm. Primary collecting veins drain into the

![Figure 21.107 Glomus tumor (vascular type). (a) Axial post-enhanced gradient echo image. Note the strong enhancement of the tumor and a thin peripheral capsule with low signal. (b) MR angiography with a strong and homogeneous enhancement of the fingertip.](image_url)

![Figure 21.108 Glomus tumor (solid type). Axial post-enhanced gradient echo image. The tumor is faintly visible on the midline. Note the peripheral low-signal capsule and the bone erosion of the dorsal aspect of the phalanx (arrow). The nail matrix is lifted up (arrowhead).](image_url)
cutaneous veins. Myelinated and non-myelinated nerves are found and may account for the pain. The tumor is surrounded by a fibrous capsule. Mucinous stroma is not rare [641]. Since all the elements of the normal glomus are present, the glomus tumor may be considered a hamartoma rather than a true tumor.

A variant with transition from glomus cells to elongated mature smooth muscle cells was described under the term of glomangiomyoma. A single case of a painful subungual lesion was described by Quaterman et al. [642].

Immunohistochemistry of glomus tumors showed the glomus cells to be positive for vimentin, a 42 kDa muscle actin (with HHF 35) and smooth muscle actin (CGA 7), and myosin [643] but negative for desmin, factor VIII-related antigen, and several neural markers; however, nerve fibers contain protein S100, Leu-7 antigen (HNK1, 110 kDa), neuron-specific enolase, and neurofilaments [644]. The endothelium clearly stains with factor VIII-related antigen, β2-microglobulin, and the lectin Ulex europaeus agglutinin (UEA) I, whereas only a few endothelial cells of the glomus tumor bind PNA, in contrast to normal nail bed vessels, the endothelial cells of which do not stain for PNA at all (E. Haneke, unpublished data). In a study of 20 glomus tumors, Daugaard et al. [643] found that the cells were also negative for fibrillic acid protein and chromogranin.

Management

The only treatment is surgical removal. Some surgeons favor the direct approach after nail plate avulsion, through the nail bed (Fig. 21.111) or the matrix (Fig. 21.112a,b) with meticulous repair. For very large lesions an H-shaped incision [645] or cruciate incision [646] might be necessary. An alternate approach is the lateral incision. The incision allows exposure to the dorsal distal phalanx (Fig. 21.113) without violating the matrix, thereby reducing the risk of postoperative deformity. The nail bed is carefully dissected from the bone until the tumor is reached and extirpated [647]. Vasisht et al. [648] reported on 19 patients using this lateral, subperiosteal approach; 15.7% experienced recurrence within 3 years, but there were no nail deformities. Extirpation is usually curative although the pain may take several weeks to disappear [649, 650]. Recurrences occur in 0–20% of cases [620, 647, ...
and may represent incomplete excision, tumor overlooked at the initial operation, or newly developed tumors [653, 654]. Most recurrences occur within months after surgery [655]. It is recommended that, if symptoms persist for more than 3 months after excision, repeat imaging and reexploration be strongly considered [656]. One must differentiate between true recurrent tumor and a new lesion, and this is not always possible. More extensive surgery than is often carried out might achieve more first-time cures [657]. Amputation of the distal phalanx is an unnecessary mutilation [627].

Blue rubber bleb nevus (Bean syndrome)
Soft papulonodular lesions (one to more than 100) resembling rubber nipples are observed. They are easily compressible and refill when pressure is released. On the hand and fingers they may be associated with leukonychia (Fig. 21.114). Somatic mutations in TEK, encoding TIE2, are found in patients with blue rubber bleb nevus syndrome. Double mutations are located on the same allele (namely in cis). In a given patient, mutations are identical in all lesions. They lead to increased activity (gain of function). The mutation T1105N-T1106P is recurrent in blue rubber nevus syndrome [658].

Angioleiomyoma
Angioleiomyomas are tumors arising from smooth muscle of a blood vessel. They are rare on the extremities and without distinctive clinical features. The final diagnosis depends upon histological identification [659].
Lebouc [434] described a case of subungual leiomyoma of the great toe. The pea-sized tumor consisted mainly of bundles of smooth muscle fibers intermingled with arterial and venous vessels. The muscular layer of the vessels was heavily hypertrophic, sometimes actually obliterating the lumen. Smooth muscle bundles were also found without vascular structures.

Conolly [660] showed a clinical and radiological picture of a leiomyoma presenting as a slow-growing tumor of the fingertip of a male aged 54 years. The authors have observed a similar case in a young woman. The distal third of the nail plate was elevated and dystrophic. After avulsion of the nail plate, a small tumor was seen directly distal to the lunula. Histology showed numerous blood vessels with a unique cushion-like hypertrophy of the smooth muscle which did not form a circular muscularis media layer. The patient had never experienced pain (E. Haneke, unpublished data).

Requena and Baran reported [661] a female presenting with a painless nodule distolateral to the distal groove with typical histology (Fig. 21.115). Baran has also observed a 70-year-old woman with extensive onycholysis of her right index finger. The pain was paroxysmal and led to the diagnosis of glomus tumor (Fig. 21.116). MRI located this tumor beneath the matrix and suggested the same diagnosis. An elliptical transverse incision enabled the lesion to be shelled out easily. It resembled grayish grains of a caviar-like substance. Histology was typical of angioleiomyoma, being composed of muscle fibers with centrally located, thin, blunt-edged, “eel-like” nuclei and eosinophilic vacuolated cytoplasm [662]. Prasad et al. reported an angioleiomyoma of the terminal phalanx in a 70-year-old lady of 15 years duration without significant bony or skin changes [663]. Bony destruction and invasion of the tumor into the medullary canal are atypical but may occur without evidence of leiomyosarcoma, as was illustrated by a 42-year-old man presenting with a painful lump on his left thumb that had been growing slowly over several months [664]. Plain radiographs revealed an osteolytic lesion of the phalanx with cortical disruption. Histology confirmed the benign character of the angioleiomyoma. Calcifications are not typical for angioleiomyoma of the skin but calcification was seen at the level of the distal interphalangeal joint in a 70-year-old woman with a 3 cm slightly painful angioleiomyoma on the distal phalanx of the second finger of the right hand [665]. Clinically it is not possible to rule out cutaneous angiolipoleiomyoma [452], a tumor that is histologically well circumscribed and composed of smooth muscle, vascular spaces, connective tissue, and mature fat cells.

Sawada [666] described a 53-year-old woman with a tender tumor of the tip of her right hallux. Upon surgery,
it was a cystic round tumor of 20 mm in the subcutis. The nail was normal. Histopathology showed an angioleiomyoma with extensive myxoid degeneration.

There are neoplasms with gradual transition from glomus cells to elongated, mature smooth muscle cells. Even so, glomangiolleiomyoma [642] is easily ruled out since there are no glomus cells in angioleiomyoma. Angioleiomyoma rarely shows malignant degeneration or metastasis. Malignant degeneration has only been reported in one digital angioleiomyoma, in a 17-year-old student [667]. MRI can help to differentiate between benign and malignant lesions with the benign being well circumscribed and delineated from the neurovascular structures and the malignant being ill defined and infiltrating the neurovascular bundle [663]. Treatment of leiomyoma of hand is surgical excision, which is usually curative.

Malignant vascular tumors

Kaposi sarcoma

Kaposi sarcoma may involve the nail unit, causing elevation or deformation of the nail plate (Fig. 21.117) [79]. König [668] described the case of a 61-year-old man with “angiosarcoma multiplex” in the distal phalanges of three toes who later developed metastases in the calf. Kaposi sarcoma caused by human herpes virus-8 (HHV-8) can involve the nail region in patients with AIDS. Kaposi sarcoma usually begins on the skin of the distal portions of the lower extremities as bluish red macules. The lesions tend to progress slowly and develop into plaques and, eventually, into nodules. An unusual expression of Kaposi sarcoma was reported by Lee and Park [572]. They presented a 61-year-old man with a rapidly growing, red-colored nodule below the distal nail plate of the right first toe. Clinically it looked like subungual pyogenic granuloma but histopathological findings were consistent with Kaposi sarcoma and immunohistochemistry for HHV-8 was positive.

Most cases described before 1920 as subungual angiosarcoma [669, 670] were probably glomus tumors. Although non-malignant, a case of acquired pincer nail associated with pseudo-Kaposi sarcoma (acroangiodermatitis) has been described by Hwang et al. [671] in a 52-year-old female patient with terminal renal insufficiency and was thought to be due to the presence of an arteriovenous fistula placed to perform hemodialysis.

Glomangiosarcoma

See the section “Glomus tumor” in this chapter.

Malignant hemangioendothelioma

These malignant tumors of blood vessels are quite rare. Three forms have been reported within the nail unit: retiform hemangioendothelioma, epithelioid hemangioendothelioma, and congenital hemangioendothelioma.

Retiform hemangioendothelioma is a locally aggressive, low-grade angiosarcoma of unknown etiology that was first described in 1994. In 2011 Keiler et al. reported an 11-year-old girl with a rapidly enlarging and intermittently painful swelling of her left distal fourth finger [672]. Physical examination revealed a non-tender enlarged distal finger pad with associated hyperhidrosis. Local recurrence is common, but no cases of distant metastasis, transformation to an aggressive vascular tumor, or tumor-related death have been observed. Surgery with clear margins, including Mohs micrographic surgery, has been considered the treatment of choice.

Epithelioid hemangioendothelioma is a borderline malignant vascular tumor that occurs mainly during the second and third decades of life. The most common symptoms are localized pain and swelling. Cases involving the nails have occasionally been reported [673–675]. The size of the tumor ranges from that of a pea to that of a plum. It is dark or bluish red, moderately soft, and non-tender. Davies et al. [673] reported on a hemangioendothelioma on the toenail bed of a patient who had worked with polyvinylchloride (Fig. 21.118a). Histology showed plump cells in a loose connective tissue stroma (Fig. 21.118b,c). Some were clumped; others formed capillary-sized channels with open lumina. Cellular pleomorphism and bizarre mitotic figures were marked and reticulin fibers were frequent. Epithelioid hemangioendothelioma developed in an arteriovenous fistula of a 61-year-old man who had undergone hemodialysis and eventually received a kidney transplant and was treated with azathioprine, ciclosporin, and prednisolone. Apart from small nodules on other fingertips, violaceous red swelling appeared under and around his right thumb nail that necrotized within 15 days. Histopathology revealed a proliferation of epithelioid tumor cells with large nuclei, obvious nucleoli, and abundant eosinophilic cytoplasm. The tumor showed multiple vascular spaces lined with a proliferating endothelium. Despite amputation of the
arm, the patient finally died from lung metastasis [676]. Londero et al. presented an impressive case of a 9-year-old boy presenting with severe pain, subungual bruises, and an angiomatous oval-shaped mass on the left thenar eminence [674]. Radiology revealed multiple osteolytic lesions in the phalanges of almost all fingers, which is in line with the assumption that the tumor usually clusters in a specific anatomic region. Kikuchi et al’s patient presented with a 6-year history of a slowly growing tumor on the dorsal surface of the ring finger of his right hand. Examination revealed an ill-circumscribed, firm, erythematous scar-like lesion associated with destruction of two-thirds of the nail plate [675]. Some cases of cutaneous epithelioid hemangioendothelioma have shown local recurrence after simple excision. Therefore, a digital amputation was performed in this case.

Congenital hemangioendothelioma is extremely rare. Only one case describing a girl with a congenital lesion on the right index finger has been reported [677]. She presented directly after delivery with a plum-like, reddish-purple, hemangiomatous lesion on the dorsum of the right index finger, which was excised at the age of 7 days.

Neuroendocrine tumor

Merkel cell tumor

Merkel cell carcinoma (MCC) is still regarded as a very rare tumor but its incidence is rapidly increasing. The Merkel cell polyomavirus (MCV) has been found associated with 80% of MCC cases [678]. MCC occurs much more frequently in severely immunosuppressed populations, and is often found on the sun-exposed skin of whites. Chronic radiodermatitis may also provoke the development of MCC [250]. MCC on the fingers has been described occasionally but mostly involves the proximal phalanx. A periungual MCC on a toe was reported in a teenage girl [679]. The tumor masqueraded clinically as granulation tissue associated with an ingrown nail. On the medial aspect of the left great toe, at the junction of the lateral nail fold and the nail bed, there was a deep red, focally ulcerated, granular nodule. On cut section of the specimen, a poorly delineated tumor consisting of brown hemorrhagic tissue and measuring 0.7 cm in diameter was identified. The tumor cells were present in dense sheets, and focally were arranged in a trabecular pattern at all levels of the dermis and in the superficial subcutaneous fat. MCC on the finger may also clinically mimic a dermatofibroma and has been reported to arise in a trichilemmal cyst in a 72-year-old white man [680]. The cornerstone for treatment is surgery. The aggressive character is emphasized by its 5-year disease-specific survival rate of about 60%. As even the smallest MCC has a 15% chance of having advanced to the lymph nodes or beyond, a sentinel lymph node biopsy should be considered. About 60% of patients respond to immune check point inhibitors such as pembrolizumab and avelumab. These agents may be most efficacious when used in the first-line setting rather than after a failure to conventional chemotherapy.

Tumors of peripheral nerves

Neurogenic tumors of the terminal phalanx are very rare.
Neuroma and Pacinian neuroma

Posttraumatic neuromas are solitary, skin-colored or pink, firm papules produced by the numerous nerve fibers in the nail bed and around the nail (Fig. 21.119). They may cause tenderness, elevation of the nail bed, and nail dystrophy. Subclinical neuroma may cause intermittent pain and tingling numbness [681]. Rashid et al. presented the case of a 46-year-old woman with a firm, tender, skin-colored subungual nodule elevating the nail plate of her second left digit. Clinically it resembled a subungual exostosis. The nodule had become tender to the touch and throbbed with pain with changes of temperature [682]. Neuroma can also be encountered in children. Egami et al. [683] reported an 8-year-old girl with a posttraumatic neuroma for 5 years. Clinically it was a dome-shaped, smooth, skin-colored and painless nodule on her fingertip. Treatment of posttraumatic neuromas is by careful resection with preservation or reconstruction of the nail bed [684, 685].

Pacinian neuroma is a benign tumor of Vater–Pacinian corpuscles, mechanoreceptors responsible for sensitivity to vibration and pressure. Pacinian neuroma generally presents in the third to fourth decade, occurring in any finger but usually involving the index and middle fingers. The etiology and pathogenesis are not clear but it has been proposed that repetitive trauma to the nerves or tendons is a precipitating factor. Volar aspects of digits, including the fingertip, are primarily affected [686] and the lesions may produce severe pain [687]. A tiny, tender, whitish papule may be the only clinical sign [688] but patients may also present with macrodactyly [689]. Simple excision is the treatment of choice for Pacinian neuroma.

So-called rudimentary supernumerary digits

The so-called rudimentary supernumerary digit is usually present at birth, often bilaterally symmetrical, and almost always located at the base of the metacarpophalangeal joint. The lesion is distinguished by the finding of multiple nerve bundles within the dermal core, especially at the proximal base of the nodule, and a large number of Meissner corpuscles in the dermal papillae. Meissner cells may be associated with the generation of cutaneous nerve plexus and nerve endings in the upper dermis, and possibly with the development of Meissner corpuscles at the early stage of rudimentary polydactyly [690]. Surgical excision is usually easy and definitively solves the problem.

Neurofibroma

Neurofibromas may occur as a solitary tumor or as part of von Recklinghausen neurofibromatosis (NF type 1). Neurofibromas are surprisingly rare in the nail region and most ungual neurofibromas are isolated and develop between the ages of 20 and 30 years. Less than 10 case reports of solitary subungual neurofibroma have been documented [691]. These neurofibromas are difficult to diagnose, particularly as they are often small and without obvious symptoms. The symptoms described ranged from onychodystrophy [692, 693] (Fig. 21.121a), subungual hyperkeratosis [311], an increase in the size of the affected digit [694], to an increase in the curvature of the nail [695]. Initially, neurofibroma may present as a blue-red discoloration of the nail plate [692]. When located in
the proximal nail fold, it may produce a longitudinal depression [79], mimic Koenen subungual tumors [696], be ulcerated and covered with telangiectasia [697], resemble a pyogenic granuloma [311, 698], or just present as a flesh-colored nodule [699].

A solitary subungual neurofibroma on the right third finger of a 13-year-old girl had deformed overall into a flattened dome shape and presented moderate tenderness from the ulnar half only. Radiography revealed mild compression atrophy of the ulnar side of the distal phalanx [700]. Longitudinal ridging and increased convexity of the lateral half of the nail with associated subungual hyperkeratosis was reported in a 27-year-old female nurse [701]. The nail dystrophy was accompanied by a diffuse, painless, non-confluent swelling beneath the proximal nail fold. Histology revealed a dermal tumor consisting of loosely arranged spindle cells with scanty, pale cytoplasm and elongated, wavy nuclei in a myxoid stroma. Chronic paronychia was the clinical presentation in a case of Fleegler and Zeinowicz [702]. MRI with injection of gadolinium shows a faintly to highly enhanced nodule of the nail bed lifting up the nail plate. Radiography may be part of the work-up in order to evaluate bone involvement [695]. As the clinical features of this tumor are non-specific, to properly diagnose and treat the tumor, complete surgical excision should be considered as the curative treatment of choice. Exploratory nail plate removal may be painful [703].

Diffuse neurofibroma of the distal phalanx of a thumb was shown to enlarge both the fingertip and the nail without causing gross nail deformity (Fig. 21.122a) [79]. Papules and associated nodules with intradermal nevi may resemble von Recklinghausen disease. They are ruled out by histopathology showing that ungual neurofibromas are virtually identical to those in other locations [704].

Plexiform neurofibromas have been reported occasionally to occur in or around the nail unit. Nambi et al. reported a 30-year-old farmworker presenting with a painless and progressive swelling of his left index finger, present since childhood. Upon dermatological examination, criteria for neurofibromatosis were present [705]. The 48-year-old patient reported by Back et al. [706] presented with a small rubbery nodule on the tip of his fourth finger but had no signs of neurofibromatosis. Between 5 and 6% of plexiform neurofibromas undergo malignant transformation, known as malignant peripheral nerve sheath tumor.

**Systematized multiple fibrillar neuromas**

These neuromas were reported by Altmeyer and Merkel in 1981 [707]. Involvement of the tips of several fingers resulted in thickening of the periungual tissue without nail plate abnormalities. No publication on this condition has appeared since then.

**Schwann cell tumor, plexiform schwannoma, and malignant schwannoma**

A Schwann cell tumor or neurilemmoma is a benign peripheral nerve tumor. They rarely occur in a subungual position [708] (Fig. 21.122) or in the proximal nail fold [709] (Fig. 21.123). Conventional schwannomas are composed of two organized cell patterns. One pattern is
more organized with a palisade appearance and an elongated, spindle-shaped cellular nucleus. The second pattern is characterized by a diffuse cellular structure with rounded nuclei. Immunostaining is strongly positive for S100 protein. Plexiform schwannoma is a rare variant of this tumor in which the Schwann cells are arranged in a plexiform pattern in the dermis and subcutis. Peripheral nerve schwannomas are a diagnostic criterion for NF type 2. Solitary schwannoma of the nail unit and subungual plexiform schwannoma may arise in children and adults, with and without NF type 2 [710–714]. Runne [715] described a case of multiple mucosal neuroma syndrome with marked thickening of the proximal nail folds which were shown to contain schwannomas. A subungual schwannoma was reported in a 49-year-old man with an 8-year history of a growing painless subungual mass, resembling pseudoclubbing [716]. A radiological examination showed bony erosion of the right distal phalangeal bone. A similar clinical and radiological picture was found in the cases reported by Wilson et al. [717] and Kulkarni et al. [718]. The latter case also presented with an almost 2 cm round and shiny tumor with telangiectasia at the fingertip. Another subungual case presented with painless nail deformation with longitudinal grooves [719]. Radiography showed mild scalloping of the distal phalanx. These cases illustrate that bone involvement may be more common in ungual schwannoma than in schwannoma elsewhere. One exceptional case described an 18-month history of a painful and ulcerating cellular schwannoma on the distal great toe of a young woman [720]. There was an ill-defined, skin-colored, soft to firm nodule in the same area. Ulceration was also present in the 3 cm sized, ancient schwannoma found in the thumb pulp of another young woman [721]. On ultrasound, schwannoma presents as an ill-defined hypoechoic subungual structure that remodels the bony margin of the distal phalanx and displaces upward the nail plate. An anechoic central area may be detected due to cystic degeneration. Low-flow arterial and venous vessels can be observed within the tumor, predominantly in the periphery [708]. Schwannomas have sharp limits and show strong enhancement of the whole or a part of the tumor on MR images. A cystic component is possible. The signal is high on T2-weighted images.

A plexiform “Pacinian” schwannoma was observed in the distal phalanx of an 11-year-old boy. The tumor was asymptomatic but hindered complete flexion of the distal interphalangeal joint. The nail plate was normal. Histology showed unusual connective tissue structures resembling Pacini corpuscles [722].

Malignant transformation of schwannomas is very rare, and malignant transformation of plexiform schwannomas has not been reported. Yamamoto et al. reported malignant schwannoma of the digital nerve in an 8-year-old boy without neurofibromatosis [723]. A pigmented cutaneous lesion extending into the nail bed of the right index finger of a 71-year-old woman was the presentation of malignant melanocytic schwannoma [724]. The superficial pigmented portion of the primary tumor consisted of epithelioid and somewhat spindle-shaped cells above the “white” spindle cell portion, demonstrating the biphasic nature of the lesion. The treatment of choice of lesions in fingers is Mohs surgery or amputation because of the difficulty of wide excision.

Granular cell tumor and malignant granular cell tumor
Granular cell tumors (GCT) are uncommon, mostly benign tumors, possibly arising from Schwann cells. They usually grow slowly, with benign behavior, with only a small minority showing malignant characteristics such as local infiltration or metastasis. GCT may occur in various sites, and cases of benign but also malignant GCT on or around the nails of fingers and toes have been published [725–728].

GCTs usually present as asymptomatic or pruritic, firm, dermal or subcutaneous papulonodules. They are
skin-colored or brownish-red, and range in size from 0.5 to 3.0 cm in diameter. Occasionally, the overlying epidermis is verrucous or ulcerated. Predilection is greatest in females, and blacks are affected several times more often than whites. The clinical picture of GCT at the nail unit depends on the position of the tumor in relation to the nail matrix or nail bed but ungual GCTs are often painful [726, 727]. Hasson et al. [729] reported a tender verrucous periungual growth located deep in the proximal nail fold of the great toe in a 35-year-old woman, producing a longitudinal groove in the nail plate (Fig. 21.124a). A linear depression was also found on the nail plate of a 69-year-old female with a matchhead-sized hyperpigmented crust on the right middle fingernail, clinically mimicking a fibrokeratoma [730]. A case presenting as painless callus at the hyponychium was reported in a 49-year-old man, resulting in deformation of the nail plate [731]. Peters and Crowe [732] described a diffuse GCT in a 33-year-old woman causing enlargement of the left middle toe, almost completely overgrowing the nail. Histology showed a well-circumscribed cluster of tumor cells surrounded by strands of collagen fibers. The tumor cells were large with round or oval and centrally located nuclei and pale cytoplasm filled with faintly eosinophilic coarse granules (Fig. 21.124b).

The first malignant GCT of the nail was reported by Urabe et al. in 1991 [725]. A reddish nodule that reached a size of 5 mm in diameter and destroyed the nail developed under the nail of the right index finger of a 51-year-old Japanese woman (Fig. 21.125a). It recurred 2 years after resection and was firm, partly eroded, and 25 mm in diameter when the finger was amputated. Multiple metastases appeared 6 months later and the patient eventually died. Histopathology of the primary and recurrent tumor (Fig. 21.125b) as well as a metastasis revealed polygonal eosinophilic granular cells with mitoses, some multinucleated giant cells, and, in the metastasis, anaplastic cells. Immunohistochemistry (protein S100, Leu 7, vimentin) and electron microscopy confirmed the diagnosis of malignant GCT.

Complete surgical resection is the treatment of choice for all GCT. The recurrence rate after adequate local excision is low, but with inadequate excision recurrence rates as high as 50% have been reported [728]. Mohs micrographic surgery may be considered when GCTs are malignant or are located in an anatomical region with limited tissue to spare.

Sironi et al. [733] reported a GCT without Schwann cell differentiation: an 18-year-old woman presented with a painful swelling in the subungual region of the terminal phalanx of the right thumb, 1 cm in diameter. The excised fragmented tissue was whitish and firm, entirely composed of plump cells with centrally placed, oval to round vesicular nuclei, with clumped chromatin and a central nucleolus and coarsely granular eosinophilic cytoplasm. The growth patterns varied from ribbons or nests, divided by fibrous septa, to bundles of elongated granular cells, more often seen at the periphery of the fragments. Mitoses and a nuclear pleomorphism were present, without necrotic areas. A diagnosis of malignant GCT was made. The ultrastructural picture was consistent with granular tumor with smooth muscle differentiation. The subsequent terminal phalanx amputation showed a subungual focus of well-differentiated leiomyosarcoma, with granular change.

**Perineurioma**

An intraneural perineurioma is a benign peripheral nerve sheath tumor with an unknown natural history that is very rare in a digit. Baran and Perrin [734] reported

![Figure 21.124](a) Granular cell tumor. Courtesy of L. Requena. (b) Granular cell tumor: clusters of tumor cells surrounded by strands of collagen fibers.)
the first case of subungual perineurioma presenting as a monodactylous clubbing (Fig. 21.126a,b). Histological study showed a myxoid tumor but with, unexpectedly, a diffuse expression of CD34, contrary to the nerve sheath myxoma.

Wortsman et al. [735] presented a 44-year-old woman with a painless subungual swelling and dystrophy of the nail, resembling fibroma or exostosis.

Sclerosing perineurioma is a rare variant of perineurioma. A case was reported in the lateral nail fold presenting as a 12 mm tumor [736]. Histological diagnosis was made after simple local excision, and showed a hypocellular tumor with an extensively collagenized stroma. Characteristic features include cords and/or whorls of small epithelioid cells and plump spindle cells. The neoplastic cells are positive for epithelial membrane antigen (EMA) and negative for S100. Ultrastructurally, the following characteristics were evident: long interdigitated cytoplasmic processes, pinocytotic vesicles, dense subplasmalemmal plaques, junctional complexes, and a discontinuous basal lamina. This study suggests that claudin-1 may serve as a helpful marker for the identification of sclerosing perineurioma.

**Osteocartilaginous tumors**

**Benign osteocartilaginous tumors**

**Exostosis and osteochondroma**

**Definition**

Subungual exostoses are outgrowths of normal bone or calcified cartilaginous remains. They are uncommon; there were only 60 subungual exostoses in a series of 6034 benign osseous lesions [737]. However, they may be
considerably underdiagnosed and underreported. A survey found more than 400 cases in the literature up to 1998.

**Etiology**
Most authors consider it to be a reactive metaplasia resulting from microtrauma [738–741] though some authors claim that a history of trauma is only occasionally found in subungual exostosis [141] (Table 21.6). The recent detection of a pathognomonic translocation t(X;6)(q22;q13-14) suggests that exostoses may be true tumors and not merely reactive lesions.

**Epidemiology**
Exostoses are particularly frequent in young people and more frequent in females than in males. Fifty-five percent of patients are younger than 18 years of age [738].

**Clinical features**
Exostoses start as small elevations of the dorsal aspect of the distal phalanx and may eventually emerge as firm and fixed tumors from under the nail edge (Fig. 21.127a) or destroy the nail plate. They exhibit a white shiny hue with telangiectasia on their surface during the early stages (Fig. 21.127b) but become more hyperkeratotic with time. Often, a collarette delineates the tumor (Fig. 21.128). The tumor usually lifts the nail plate (Figs. 21.128, 21.129a), resulting in onycholysis or nail plate deformity. Subungual exostoses are almost invariably solitary, with only rare reports of bilateral lesions [742]. The vast majority of exostoses involve the toes, with an obvious predilection for the great toe (70–80%) [743]. They are mostly located on the dorsomedial aspect of the tip of the great toe, though subungual exostoses may also occur in lesser toes [739, 744–747] or less commonly thumb, index finger, or other long fingers [330, 748] (Fig. 21.129a). Carroll et al. [749] reported a series of 16 cases of subungual exostosis in the hand. Only 42 positively identified cases have been found in the literature to date [739, 741, 750–752]. Bilateral exostoses of the great toenails have been reported as the discovery of a bony ridge parallel to the hyponychium during surgery for typical congenital malalignment of the great toe nails.

**Table 21.6** Differential diagnosis of subungual exostosis and osteochondroma.

<table>
<thead>
<tr>
<th>Feature</th>
<th>Subungual exostosis</th>
<th>Subungual osteochondroma</th>
</tr>
</thead>
<tbody>
<tr>
<td>Etiology</td>
<td>Trauma, repeated microtrauma, infection</td>
<td>Congenital or traumatic</td>
</tr>
<tr>
<td>Onset</td>
<td>Adolescence, young adults</td>
<td>10–25 years</td>
</tr>
<tr>
<td>Male : female ratio</td>
<td>1 : 2</td>
<td>2 : 1</td>
</tr>
<tr>
<td>Location</td>
<td>Distal end of distal phalanx</td>
<td>Juxtaepiphyseal</td>
</tr>
<tr>
<td>Growth rate</td>
<td>Moderate</td>
<td>Slow (occasionally rapid)</td>
</tr>
<tr>
<td>Radiology</td>
<td>Broad-based trabeculated bone with distal flare</td>
<td>Sessile bone with scalloped dome and radiolucent hyaline cartilage cap</td>
</tr>
<tr>
<td>Growth direction</td>
<td>Distally and away from the epiphysis</td>
<td>Slanting away from the adjacent interphalangeal joint</td>
</tr>
<tr>
<td>Histopathology</td>
<td>Cancellous bone with fibrocartilaginous cap</td>
<td>Bone with hyaline cartilage cap</td>
</tr>
<tr>
<td>Malignant degeneration</td>
<td>None in isolated cases, 3–5% in hereditary multiple exostoses</td>
<td>Rare (1%)</td>
</tr>
<tr>
<td>Treatment</td>
<td>Complete removal</td>
<td>Complete removal</td>
</tr>
</tbody>
</table>

*Source: Schulze and Hebert [771]; Davis and Cohen [739]; Murphey et al. [742], Lee et al. [761]. Reproduced from Schulze and Hebert [771] with permission of John Wiley & Sons.*
in an 8-year-old boy [753]. James [754] reported a case arising from the ventral aspect of the distal phalanx of the left index finger and causing enlargement of the fingertip. Proximal nail groove pain associated with bilateral exostoses on the proximal medial aspect of the base of the distal hallux phalanges is unusual [755].

**Differential diagnosis**

Exostosis may mimick subungual pyogenic granuloma-like outgrowth [756], suggesting an ingrown toenail (Fig. 21.130), a subungual wart [757], or even a melanoma [758]. Recurrent episodes of bleeding have been reported [759] but this is not typical for subungual exostoses.

Whether or not subungual osteochondroma [760] is a different entity is still not clear [742, 744, 761]: subungual osteochondromas and subungual osteocartilaginous exostoses share the same clinical picture, same biological behavior, some radiographic features, and benefit from the same treatment but pathologically represent distinct entities. Norton [141] and Lee et al. [761] listed differential features between subungual osteochondromas and subungual exostoses (Table 21.7). Lemont and Christman [762] presented a classification for subungual exostoses, in genetic and acquired types. This was based on the lesion's pathology, radiographic appearance, location, and age. They stated that the genetic subungual exostosis (type I) appears in the second and third decades of life, paronychia is frequent, and only the medial aspect of the nail bed is hypertrophic. The acquired subungual exostosis (type II), in their study, is observed from the fourth through to the sixth decade of life with a blunt or sharp protuberance at the distal and dorsal aspect of the distal phalanx, without cartilage. The nail plate appears as an inverted U, with nail bed hypertrophy being apparent. In fact, this classification describes the osseous changes
seen in pincer nails, with type I being the inherited, usually symmetrical type of overcurvature, and type II characterizing the acquired type of pincer nails [763]. This type of osteophyte formation is equivalent to what is called subungual hyperostosis.

Medical imaging
Dermoscopy most commonly shows vascular ectasia (70%), followed by hyperkeratosis (60%), onycholysis (40%), and ulceration (30%) (Fig. 21.131) [764]. Radiography confirms the diagnosis, and should be performed prior to any biopsy or invasive procedure. The exostosis is an ill-defined, trabeculated, osseous growth (Fig. 21.129b) with an expanded distal portion covered with radiolucent fibrocartilage. In contrast to osteochondromas, the bony excrescence usually appears in the tip of the phalanx, distal to the physeal scar, as opposed to the radiodense projection in subungual osteochondromas that appears at the union of the distal with the middle thirds of the phalanx [765]. Furthermore, there is typically no continuity with the underlying cortex and medullary canal, and the cartilage cap consists of fibrocartilage rather than hyaline cartilage. Unlike most osteochondromas in this region they are not associated with growth deformities. The base of the lesion may be broad or narrow. The cartilage cap is typically larger than the base and may be either indistinct or well demarcated [742].

CT scan and MRI are rarely indicated but MRI is the best modality for visualizing the effect of the lesion on surrounding structures and evaluating the hyaline cartilage cap [742]. Proton density-weighted or gradient echo images are the most accurate and can distinguish hyaline cartilage with high signal (Fig. 21.132) from fibrocartilage with lower signal. These two components may be associated and the thickness of the cap can be accurately measured. The trabecular bone is nicely visible on gradient echo images, where the trabecular network is increased by magnetic susceptibility artifacts.

Diagnosis
The triad of pain (the leading symptom, present in 77% of all patients with subungual exostosis [738]), nail deformation, and radiographic features is usually diagnostic.

Evolution
Solitary subungual exostoses have never been observed to undergo malignant degeneration.

Pathology
Histology shows a proliferative fibrocartilaginous cap that merges into hyaline cartilage, forming mature trabecular bone at its base by enchondral ossification. It appears

Table 21.7 Differential features of exostosis, osteochondroma, enchondroma, and epidermoid cyst.

<table>
<thead>
<tr>
<th>Tumor</th>
<th>Age (years)</th>
<th>Sex ratio</th>
<th>History of trauma</th>
<th>Rate of growth</th>
<th>X-ray</th>
</tr>
</thead>
<tbody>
<tr>
<td>Exostosis</td>
<td>20–40</td>
<td>F : M 2 : 1</td>
<td>Occasionally</td>
<td>Moderate</td>
<td>Trabeculated osseous growth with expanded distal portion covered with radiolucent fibrocartilage</td>
</tr>
<tr>
<td>Osteochondroma</td>
<td>10–25</td>
<td>M : F 2 : 1</td>
<td>Often</td>
<td>Slow</td>
<td>Well-defined sessile bone growth with hyaline cartilage cap</td>
</tr>
<tr>
<td>Enchondroma</td>
<td>20–40</td>
<td>M + F</td>
<td>Often</td>
<td>Rapid</td>
<td>Lobulated bone cyst showing radiolucent defect, bone expansion, and flecks of calcification</td>
</tr>
<tr>
<td>Epidermoid cyst</td>
<td>8–83</td>
<td>M : F 2 : 1</td>
<td>Almost always</td>
<td>Rapid</td>
<td>Radiolucent cyst: no calcification</td>
</tr>
</tbody>
</table>

Source: Reproduced from Norton [141] with permission from Elsevier.
probable that the cartilaginous cap is finally replaced by bone in mature lesions. Electron microscopy reveals that the tumor is composed of two types of cells, one rich in cell organelles including rough endoplasmic reticulum, well-developed Golgi apparatus, and glycogen granules, the other with few such cell organelles. The former cells seem to be osteoblasts actively engaged in bone formation, and the latter osteocytes related to those situated deeper in bone matrix of normal bone. However, ossification or calcification in subungual exostosis is rather casual, and osteocytes in this disorder may lack the capacity to elaborate compact bone.

**Management**

The principle of treatment is to achieve complete excision of the lesion, under full aseptic conditions, by curetting or burring down to normal trabecular bone while minimizing deformity to the nail plate. A different approach in patients with protruded subungual exostosis and non-protruded subungual exostosis has been promulgated. According to these authors, in patients with a protruded subungual exostosis, the mass should be removed by a dorsal approach with the removal of the nail, and injury to the nail bed should be repaired. In patients with a non-protruded subungual exostosis, the mass should be excised through a "fish-mouth" type incision at the toe tip. There is often a postoperative discrete distal onycholysis. The recurrence rate has varied between 0% and 53%. Multiple recurrences of assumed subungual exostosis in a finger could be a presentation of a Nora's lesion (bizarre parosteal osteochondromatous proliferation), although Nora's lesions may also be found in the toe.

**Hereditary multiple exostoses**

(familial osteochondromatosis, multiple exostoses syndrome, diaphyseal aclasis, multiple osteochondromas)

Hereditary multiple exostoses (HME) is an autosomal dominant heritable disorder, mapped to the exostoses genes (EXT). HME affects the enchondral skeleton during the period of growth in a variety of ways, but generally "close to the knee and far from the elbow." It usually occurs between 2 and 10 years of age but most cases are seen by 4 years of age. It is characterized by thickening and deformity of the growing bone with the formation of numerous cartilage-capped exostoses clustered around the areas of most active growth, and by the development of multiple osteochondromas. Also shortened nails caused by onychoatrophy, brachydactyly, or nail plate malalignment have been reported. The unlar side and bones around the metacarpophalangeal joints are most commonly affected. Presentation at an older age is illustrated by a 16-year-old boy who presented with anonychia of his left index finger caused by a firm non-tender nodule affecting the proximal two-thirds of the nail bed and the lunula, with resultant slight elevation of the proximal nail fold. The outgrowth had started 2 years earlier. A lateral radiograph revealed an exostosis. His sister, aged 12, presented with multiple exostoses of the hands, clearly visible radiologically. They were located on the ventral aspect of the middle phalanx of the right index finger and the dorsal aspect of the distal phalanx of the right fifth digit and the first, second, and third left digits where they slightly lifted up the nail plate.

Laugier et al. reported two cases in the French literature. In the first, exostosis of the base of the distal phalanx of the fourth finger of a 10-year-old boy resulted in a lateral deviation of the nail plate. Several fingers were affected in an 11-year-old girl presenting with various physical signs, including a bump at the base of the right index nail, overcurvature of the lateral aspect of the nail of the right middle finger, a red linear longitudinal line with a distal fissure on the right fifth fingernail, and distal fissures arranged in a fanwise manner on two other nails.

**Figure 21.133** (a) Multiple exostoses syndrome: proximal bony swelling with anonychia. (b) Radiological appearance of (a).
Hazen and Smith [774] reported prominent elevation of the proximal portion of the nail and corresponding nail fold of several fingers by firm and non-tender nodules. A similar picture was seen in a 7-year-old boy with an enlarging nodule on the ulnar aspect of the left ring fingernail fold and nail plate [779]. Schmitt et al. [775] reported three young children with lifting up of the nail plate which was fissured and covered with longitudinal ridges. In Del-Rio et al.'s report [773], nail plate deformity consisted of malalignment, longitudinal dystrophy, and swelling of the proximal nail fold on several fingers that had developed slowly since birth.

When the disease involves the distal phalanx, it most often seems to affect several digits simultaneously [776]. Although the estimated risk of malignant transformation in HME has varied within studies, the majority of researchers agree that the lifetime risk is between 1% and 2% [742, 780].

**Soft tissue chondroma**

Soft tissue chondroma is a rare, benign, cartilaginous tumor that is not attached to the underlying bone. It mainly occurs on the hands or feet of individuals aged between 30 and 60 years [781] but may also present at a younger age [782, 783]. It commonly presents as an asymptomatic slowly-growing mass. Over time patients complain of symptoms such as local tenderness and pain on action. Swelling of the distal phalanx of the middle finger with progressive distortion of the nail was seen in a 37-year-old man. MRI revealed a 9 × 11 mm large, well-defined tumor in the nail bed and matrix. At operation, a bluish oval lesion was easily dissected from the surrounding tissue. Histology revealed fairly normal mature hyaline cartilage [784]. Two more nail bed chondromas were described by Lichtenstein and Goldman [785]. Distal erythronychia with a firm, immobile nodule of the right index finger pad was the presenting sign in a further case [786]. Another patient with marked finger and nail deformity was reported by Ishii et al. in 2010 [787]. MRI is the method of choice in the evaluation of this entity. Histology is often required for the correct diagnosis, because cytology will show worrying cell atypia [781]. Treatment is recommended only for patients who have persistent pain or cosmetic concerns such as nail deformity. There is a relatively high rate of local recurrence of 15–25%.

**Enchondroma**

Solitary enchondroma accounts for 90% of all bone tumors of the hand but is rare in the distal phalanx. The tumor arises in the medullary cavity and grows into the cortex, forming a prominent endogenous mass in the bone. Though occurring in all age groups [788–790], it is most frequently seen between 30 and 35 years of age. Occasionally patients present with multiple enchondromas (enchondromatosis). Ollier disease and Maffucci syndrome, the most common enchondromatoses, are discussed in “Enchondromatosis”. Enchondroma is frequently asymptomatic but may enlarge and become a painful tumor that expands the tip of the finger (Fig. 21.134a). Pathological fracture as a result of continuous thinning of the bone cortex is frequently the presenting symptom. It may also present clinically as paronychia [791–793], as clubbing with thickening, discoloration, and longitudinal

Figure 21.134 (a) Enchondroma. (b) Radiograph showing expansion of the distal phalanx and irregular, spotty calcification (see (a)). (c) Enchondroma: hyaline cartilage proliferation with irregularly arranged cells (see (a,b)). Courtesy of G. Rassner.
ridging of the nail [794, 795], or as a pearly-white tumor lifting the overlying nail plate [796]. In a case series of 34 patients with enchondroma in the distal phalanx of the finger the presenting initial symptoms included pain in 44%, a clubbing finger deformity in 26%, an infection in 18%, and a mallet finger deformity in 12% [790]. Radiologically, 29% of these cases had cortical thinning and enlargement, 35% had unilateral bone cortex defects, and 18% had bilateral bone cortex defects (both volar and dorsal sides). Radiography may sometimes reveal spotty calcifications [196] (Fig. 21.134b). The enchondroma is typically located at the base or in the middle of the distal phalanx abutting the articular surface [505].

Enchondroma involving the distal phalanx of the hand was monostotic in three cases and polyostotic in 30 cases in Takigawa’s review [797]. Histology shows hyaline cartilage proliferation with irregularly arranged cells (Fig. 21.134c). Although enchondromas of the hands and feet often show cytological features suggestive of malignancy, the biological behavior of these tumors is usually benign. The risk of developing a chondrosarcoma from an enchondroma is estimated to be about 4% [798, 799] but is higher in individuals with enchondromatosis. Clinically, the presence of non-mechanical pain or night pain is cause for concern and further immediate investigation is indicated. Pain located in the nail bed will be present in most patients, as it is with benign enchondroma [800]. Therefore, treatment will be the rule but not all lesions necessarily need treatment as a certain degree of spontaneous healing may take place in some cases. Surgical resection and curettage with cryotherapy are options [788, 790, 801]. Recurrences after surgical resection are rare.

**Enchondromatosis: Ollier disease and Maffucci syndrome (or chondrodysplasia with multiple soft tissue hemangiomas)**

Ollier disease is a non-hereditary syndrome that results from cartilage failing to undergo normal ossification in an asymmetrical fashion (Fig. 21.135). It is a rare condition, characterized by multiple enchondromas appearing in childhood. Maffucci syndrome combines the features of Ollier disease associated with vascular lesions. Both diseases are associated with somatic mutations of isocitrate dehydrogenase 1 or 2.

Patients with Ollier disease may present with onycholysis and nail dystrophy related to a subungual enchondroma [802], or with thick fingers due to the enchondroma [803]. The diagnosis of Ollier disease is based on clinical features and radiographs that show multiple radiolucent lesions in the metaphyses [804].

Maffucci syndrome is a rare disease involving multiple enchondromatosis and vascular tumors of the dermis, subcutis, or internal organs which develop in childhood, with up to 25% being affected at birth or during infancy. These vascular lesions may be venous malformations, spindle cell hemangiomas, or, sometimes, lymphangiomas. They are usually located adjacent to areas of enchondromatosis and present as bluish nodules. Radiographic appearances are nearly pathognomonic, with multiple enchondromas seen associated with soft tissue swelling and phleboliths. The hands particularly develop vascular hamartomas with an asymmetric distribution, often showing cauliflower-like growths. Gross skeletal deformities are due to masses and columns of uncalcified cartilage causing unequal growth of bones and delayed healing of the easily sustained bone fractures. The hands and feet may be transformed into useless masses [805, 806]. This condition is an important congenital cause of macrodactyly, which may be the presenting sign [807].

Involvement of the terminal phalanx may result in gross deformity, dystrophy, or loss of the nail (Fig. 21.136) [808, 809]. A violaceous discoloration, most likely a hemolymphangioma, underneath the right third fingernail, was present in an 8-year-old girl [810].

The differential diagnosis of subungual chondroma [811] includes most tumors occurring in a subungual location, such as subungual exostosis, pyogenic granuloma, common wart, glomus tumor, epidermoid cyst, keratoacanthoma, melanoma, neurofibroma, and sarcoma, but the distinction between chondroma and low-grade chondrosarcoma is one of the most difficult to make histopathologically [812]. A case of subungual melanoma with cartilaginous differentiation was described by Cachia and Kedziora [813].

Malignant transformation of enchondromas to chondrosarcomas is common in individuals with multiple enchondromas, as in Ollier or Maffucci syndrome where the risk approaches 25% and 100%, respectively [800, 814], but evolution to other malignant neoplasms has also been observed [809].
Osteoid osteoma

Osteoid osteoma [815] is a distinct clinical and pathological entity [816]. About 8% of all osteoid osteomas occur in the phalanges, and 1–2% of hand tumors are osteoid osteomas; however, location in the distal phalanx is quite rare [817] with index predominance. The usual incidence ratio is three males to one female [818]. Osteoid osteomas typically appear in children, adolescents, and young adults [818–821]. Szabo and Smith [822] reported one case that had probably existed since birth.

Osteoid osteoma is a benign osteoblastic lesion causing swelling of the distal phalanx or even enlargement of the entire tip and clubbing. Thickening or enlargement of the nail may be associated (Fig. 21.137a). Osteoid osteoma usually evokes a “nagging” pain, accentuated at night, which is poorly localized and may extend proximal to the proximal joint of the affected digit. Local tenderness is present in about one-half of the cases. There is no evidence of inflammation but warmth and swelling may be present, suggesting osteomyelitis [823]. Relief of pain by salicylates and other non-steroidal antiinflammatory drugs (NSAIDs) is characteristic [824]. However, symptoms may vary considerably. A case of a painless nail bed osteoid osteoma with upward lifting of the nail plate has also been reported [825]. The skin is either normal in color or faintly violaceous. Increased sweating of the area has been described. Palpation with a blunt probe may help to localize the tender tumor on pressure. A nidus, characterized by a small area of rarefaction with surrounding sclerosis, is demonstrable radiologically in most cases and has been likened to a sleigh-bell [826, 827] (Fig. 21.137b); it is located in the medulla, in the cortex, or subperiosteally with a very thin covering of bone over the nidus [828]. The hypervascularization explaining the nail thickening can be demonstrated by arteriography [828, 829], by thermography [830], or by scintigraphy [831]. The differential diagnosis comprises glomus tumor, implantation epidermoid cyst, sclerosing osteitis of Garré, localized cortical bone abscess, syphilitic dactylitis, tuberculosis, chondroma, and arteriovenous fistula. It is not possible to differentiate between osteoid osteoma and benign osteoblastoma (less painful, less sclerosis) on histological grounds alone (Table 21.8).

Computed tomography (CT) with thin contiguous slices is the best imaging technique to analyze and accurately
locate the nidus, previously guided by a bone scan. MRI is less sensitive than CT for the detection of a tiny intracortical nidus. The osteoid tissue is quite intense on gradient echo images and enhances. The large inflammatory reaction of the nail bed is very difficult to see with CT, although it is obvious with MRI, as associated medullary edema of the distal phalanx (Fig. 21.138). A synovitis of the distal interphalangeal joint may be associated. Young patients may have premature fusion of the adjacent epiphysis.

Histologically, the nidus [832] is a meshwork of osteoid trabeculae with varying degrees of mineralization in a background of vascular fibrous connective tissue. When osteoid osteomas appear in the distal phalanx, they present unusual diagnostic difficulties due to the atypical radiological appearance, the presence of soft tissue enlargement and nail deformity, the small size of the distal phalanx, and consequent close approximation of lesions to the nail, growth plate, and distal interphalangeal joint [833].

The natural history is regression within 6–15 years without treatment; however, this can be reduced to 2–3 years with the use of aspirin and NSAIDs [818]. Surgical treatment is by en bloc resection through a fish-mouth incision [834]. Curettage may fail to eradicate the lesion but destructive techniques are used more frequently than in the past [818]. Percutaneous CT-guided ablation with laser or radiofrequency has now widely replaced surgery as the treatment of choice for osteoid osteoma of long bone lesions [835, 836] and is also used in fingers [837, 838]. However, surgical excision still plays a major role for lesions in the hands and feet owing to the close relationship of the small bones with the neurovascular structures. Radiography does not seem to be helpful in deciding whether the whole lesion has been removed. After therapy, the swelling regresses, a normal nail regrows, and the pain gradually disappears. There are cases, however, where digital enlargement persisted after removal of the lesion. Therefore, reducing the soft tissue and narrowing the nail at the same time as the lesion is removed has been advocated [839].

Giant cell tumor of the bone
Giant cell tumor of the bone is a rapidly growing, locally aggressive, and destructive neoplasm with a tendency for local recurrence after curettage. Giant cell tumor is typically but not exclusively seen in patients 20–40 years of age. Its appearance in the hand and foot is uncommon but involvement of the distal phalanges has been reported in several case reports [840–847]. One case has been described in a young female with Goltz–Gorlin syndrome [848]. The lesions that present in distal phalanges tend to be in younger patients and are more aggressive than giant cell tumors in the long bones [849]. The most common complaint is pain that may be noted suddenly, following relatively mild trauma [842, 844, 847]. A painful lesion is always tender to palpation with sometimes a palpable bony mass at the site of the lesion. A grossly enlarged distal phalanx and nail may be present [847, 850]. The radiographic appearance of giant cell tumor in the tubular hand bones is variable and non-specific but expansile osteolytic lesions which, by the time of diagnosis, generally involve most of the phalanx or the whole of

<table>
<thead>
<tr>
<th>Osteoid osteoma</th>
<th>Osteoblastoma</th>
</tr>
</thead>
<tbody>
<tr>
<td>Size</td>
<td>&lt;1 cm in diameter</td>
</tr>
<tr>
<td>Symptoms</td>
<td>Painful</td>
</tr>
<tr>
<td>X-ray</td>
<td>Considerable reactive bone and sclerosis</td>
</tr>
<tr>
<td>Location</td>
<td>Long bones</td>
</tr>
<tr>
<td>Histology</td>
<td>Indistinguishable</td>
</tr>
</tbody>
</table>

Table 21.8 Differentiation between osteoid osteoma and benign osteoblastoma.
Chapter 21

the metaphysis, or epiphysis, of affected metacarpal bones, have been reported. Fracture of the cortex or complete destruction of the bone may be observed. Stippling or calcification within the tumor has not been reported. On MR images, the signal behavior of the tumor is identical to that of the surrounding soft tissues (Fig. 21.139). However, the lesion may have numerous cavities with high signal if there is an aneurysmal component.

Histological examination of the tissue will be necessary for definitive diagnosis and to discriminate between other giant cell containing lesions, such as an aneurysmal bone cyst, and giant cell reparative granulomas. Histologically giant cell tumor is described as a background of mononuclear stromal cells with many multinucleated giant cells, which appear similar to osteoclasts, leading to the initial description of the tumor as an osteoclastoma [851].

A 13-year-old child developed a lesion on her third toe some months after cryotherapy for warts. This was curetted but recurred rapidly. It was then seen as a round, yellowish, soft tumor in the distal nail bed, which was tender on palpation. Radiography showed osteolysis and MRI revealed a phalangeal tumor invading the dermis. The lesion was removed with part of the terminal phalanx. Histology showed a tumor invading and fragmenting the underlying bone. The tumor cells had an eosinophilic cytoplasm and large nuclei with obvious nucleoli, thus resembling histiocytes. There were many multinucleated giant cells, but neither atypical cells nor mitoses were seen [852].

Since there is an 18% incidence of multicentric foci of giant cell tumors of the hand, bone scan is advised when these tumors occur in the hand [844].

The tumor tissue is vascular, friable, and reddish-brown. (Fatal) metastasis of giant cell tumors of bone is very rare but is reported [840]. Surgical therapy is the most often used treatment for phalangeal giant cell tumor. Amputation is not always necessary. Curettage as a monotherapy was found ineffective as a method of treatment [844]. Cryotherapy has been recommended; it carries risks of neuropraxia, skin necrosis, and stiffness but has been used with success in combination with curettage and cementation. Recently, denosumab, a monoclonal antibody that targets the activator of the NFκB receptor, has been shown to be very effective in treating giant cell tumors of bone [853].

Malignant osteocartilaginous tumors

Chondrosarcoma
See the section on “Sarcomas” in this chapter.

Synovial tumors

Giant cell tumor of tendon sheath
(benign synovialoma, benign xanthomatous giant cell tumors, villonodular pigmented synovitis)

The membrane around the joint is called the synovial membrane, and synovia is the fluid in the joint. Therefore, the correct term for these tumors would be synovialoma. However, the term synovioma is used more frequently. Giant cell tumor is a neoplasm derived from the tendon sheath or joint synovial membrane. It is the second most common subcutaneous tumor of the hand and is more frequent in females than in males. On the digits (Fig. 21.140) it usually occurs on the dorsum of the distal interphalangeal joint and appears as a solitary, often lobulated, slow-growing, skin-colored, and smooth-surfaced nodule which tends to feel firm and rubbery. The tumor, which may present as multiple nodules [854], may enlarge to the size of a cherry and may cause pain on flexion by virtue of its dimensions. Only rarely does the tumor interfere with the nail unit. In the region of the lateral nail fold, periodic inflammation and drainage may occur [855]. In contrast to malignant synovioma, no calcification is demonstrable on radiography [856].
Very few cases of subungual giant cell tumor have been published. Abimelec et al. [857] reported a 41-year-old man who had observed abnormal growth of his left ring fingernail. This was due to a firm, non-inflammatory swelling of the matrix region. Another giant cell tumor involving the lateral nail fold and nail bed and interfering with nail growth was seen in a 37-year-old man [858].

The case of Richert et al. [858] involved the lateral groove and was lifting up the nail bed and plate (Fig. 21.141a). Two cases, both in women, presented with a cystic-appearing lesion causing a wide longitudinal groove in the nail plate [859, 860].

MRI may suggest the diagnosis with a nodule close to the distal insertion of the flexor or extensor digitorum tendon or to the synovium of the distal interphalangeal joint. In typical cases, hemosiderin deposits lead to typical signal void artifacts on all MR images (Fig. 21.141b). These deposits are less often visible in the fingers than in the knee. However, intermediate to low signal of a part of the tumor is very frequent and must evoke the diagnosis. On the other hand, signal enhancement after the injection of gadolinium is not specific.

Histopathology (Fig. 21.140b) shows a cellular tumor composed of histiocytic and fibroblastic cells with a variable number of giant cells and some foam cells in a hyaline stroma. Siderophages may give the tumor a brown appearance.

Differential diagnosis includes a ganglion, which tends to feel more cystic (aspiration or transillumination), fibroma of tendon sheath [861, 862], implantation epidermal cyst, fibrokeratoma, rheumatoid nodule, multicentric reticulohistiocytosis, metastatic tumor, tendinous xanthoma, chondro- or osteosarcoma, and reticulohistiocytoma, whose histology may be identical to that of giant cell tumor. Granuloma annulare (Fig. 21.142) and erythema elevatum diutinum (Fig. 21.143) should also be ruled out.

Treatment is by careful surgical removal. An oblique incision along the longest axis of the tumor enables the multilobulated lesion to be exposed. It may penetrate the extensor tendon. The tumor often exhibits a suggestive orange hue. Complete removal is necessary to prevent recurrences.

Figure 21.140 (a) Giant cell tumor: benign synovioma. Courtesy of H.H. Wolff. (b) Giant cell tumor: mainly histiocytic and fibroblastic cells, some giant cells and foam cells in a hyaline stroma.

Figure 21.141 (a) Giant cell tumor involving the lateral groove. (b) Giant cell tumor of the sheath of the flexor digitorum profundus tendon exhibiting hemosiderin deposits (arrows). Sagittal gradient echo image.
Lipomatous and myxomatous tumors

Lipoma
Lipomas are subcutaneous tumors composed of fat tissue, and are most commonly found on the trunk. Stein [441] described a lipoma of the distal phalanx of the thumb causing a tender and painful swelling and destruction of the distal bony phalanx. A massive and rapidly expanding but painless lipoma without osseous invasion was reported to cause a toe to become approximately 10 times bigger than before in two patients [863, 864]. However, bone erosion was observed in another patient and extended into the medullary space with a sclerotic peripheral margin [865]. A fibrolipoma presented as a 3 cm firm soft tissue lump arising from the third toe pulp in a 42-year-old man and resulted in amputation of this toe because MRI suggested atypical lipoma or differentiated liposarcoma [866]. Another clinical expression was seen in a 40-year-old woman with subungual swelling of the second left finger with thinning, dystrophy, and hyperconvexity of the nail [867]. A traumatic origin of subungual lipoma has been reported [868] and might also have played a role in a cook with a subungual spindle cell lipoma on the right thumb [869]. The latter presented with a mass that was painful with pressure and a red lunula, a bulge in the central nail plate, and distal onycholysis due to the proximal subungual mass. Longitudinal erythronychia with distal splitting of the nail plate can also be a presentation of subungual lipoma [870]. Baran reported a lipoma [871] located in the lateral nail fold of a finger. The tumor underwent slow growth. Histologically it resembled nevus lipomatodes superficialis. A subungual lipoma was seen in the right thumb of a 73-year-old woman. Interestingly, there was a squamous cell carcinoma of the nail bed overlying this lipoma [279]. Richert et al. [872] reported three additional cases in 2004, two of which had histopathological features of perisudoral lipomas.

A subungual lipoma of the ring finger [873] deformed the nail, which became hemispherical with ridging and loss of luster. The tumor mimicked a fibroma (Fig. 21.144a,b). Lipoma is easily recognized on MR images as a mass with a very intense signal on T1-weighted images. The signal is canceled with fat suppression presaturation.

Superficial acral fibromyxoma
(myxoma, digital fibromyxoma)

Definition
Superficial acral fibromyxoma (SAFM), formerly known as myxoma, is an increasingly frequently occurring soft tissue tumor with a striking predilection for the subungual or periungual region of the hands and feet [874] (Fig. 21.145a–c). It affects mostly adults, but cases have been reported between the ages of 4 and 86 [874–878]. Patients may present with a history of 3 months to 30 years.

Etiology
The etiology is so far unknown. Only one case reports an SAFM arising 2 years after injury [879].

Clinical features
Almost all SAFM are located in the peri- and subungual areas. The nail bed is affected in about half of the cases.
SAFM is a slow-growing, solitary, erythematous, elastic tumor [343]. The lesion is often asymptomatic, but pain may occur in about 40% of cases [874]. The tumor may progressively distort the nail apparatus from nail bed, folds, or matrix involvement [796, 880–883]. The surface is described as dome-shaped, verrucous, or polypoid [884]. It may also have white, pink, and red components [885, 886]. The mean size of an SAFM is approximately 1.75 cm, although lesions documented in the literature have ranged from 0.5 to 5.0 cm in diameter. Submatrical localization has been reported exceptionally and presented as pseudoclubbing, isolated onychogryphosis, and a triangular macrolunula [881, 887]. A single case of SAFM presenting as a hemorrhagic pigmented streak on the toenail has been reported in a woman with Fitzpatrick skin type VI and a verrucous subungual mass [888].

**Medical imaging**
Radiography shows bone erosion in 3% of cases [874]. Ultrasound shows a hypoechoic, inhomogeneous tumor with necrotic zones and variable vascularity on color Doppler [889].

**Histology**
An (incisional) biopsy is required to reveal the true nature of the tumor, although fine needle aspiration cytology has been used as well [890]. Histologically the lesions are well-circumscribed but not encapsulated dermal nodules composed of stellate and spindle cells, arranged in a myxoid matrix [877]. In three of the 12 cases of Fanti et al. marked hyperkeratosis and acanthosis of the overlying epidermis were present but there was no connection with the overlying epidermis [891]. Cartilaginous and osseous metaplasia have been reported [874]. Loss of Rb1 immunosuppression was observed in 90% of cases in one study in 11 patients [892]. This suggests a relationship of SAFM to the Rb1-deleted tumor family. Very low grade atypia and a few mitotic figures can be found in a few cases. Cells show immunoreactivity for CD34 and CD99 but only focally positive or completely negative staining is shown for EMA. Actin, S100 protein, HMB45, and cytokeratin are negative [885]. SAFM poses a diagnostic problem for pathologists, resulting in misclassification and overtreatment [874]. The differential diagnosis includes a group of neoplasms in which myxomatous change is a prominent secondary feature and a variety of conditions characterized by mucinous degeneration of the skin or soft tissues [880, 893]. The distinction between SAFM and malignant myxoid tumors is important since the latter often have a protracted clinical course characterized by multiple recurrences and metastasis [874]. Armijo [879] listed the salient differences between cutaneous myxoma and myxoid cyst. Cellular digital fibroma (CDF) also mimics SAFM histopathologically [894]. Histopathologically, both SAFM and CDF can be characterized by spindle to stellate cells arranged in a storiform or fascicular pattern with variable degrees of myxoid background stroma. Accentuated microvasculature and conspicuous mast cells are potentially suggestive of SAFM; meanwhile, keratin horn and epidermal collarette are commonly observed in CDF.

**Management**
Exirpation of the lesion is usually easy as the tumor is well demarcated (Fig. 21.145d–f). Complete excision is mandatory to prevent local recurrences. Hollmann et al. reported that in the evaluation of 73 tumors 89% had positive margins, displaying the ability of the tumor to interdigitate with normal tissue. Despite inability to achieve negative margins with high success, recurrence has been reported to be only approximately 20–25% and only to occur in cases with positive margins [874]. In order to prevent recurrences Mohs surgery has been advocated [895].

**Evolution**
SAFM has a benign behavior, and malignant transformation has not been described [874].
Sarcomas

Sarcomas arising in the fingertip are very rare. The disease has usually been present long before the diagnosis is made and the lesion treated; a very painful oozing growth sheds the nail plate or grows out from under the nail.

Phalangeal sarcoma

Phalangeal sarcoma with osteolytic lesions may enlarge the distal phalanx to three times its normal size and present with a warm and extremely painful clinical appearance, similar to a paronychia [896]. A case of osteogenic sarcoma arising in the distal phalanx of the thumb of a dentist after chronic intermittent exposure to X-irradiation is unique [897]. Keratotic material progressed and gradually replaced two-thirds of the nail bed. Metastases to regional lymph nodes occurred very early. Therefore, excisional biopsy of the entire ulcerating lesion is the only effective treatment. Due to its rarity, osteogenic sarcoma is not often considered in the differential diagnosis of phalangeal tumors.

A low-grade myofibroblastic sarcoma of the distal phalanx of the ring finger was reported in a 51-year-old woman presenting with a 12-month history of a painless and slowly growing mass [898]. Radiographic studies showed a destructive lytic lesion in the distal phalanx with soft tissue extension. Pre- and post-contrast MRI showed a tumor in the ring finger distal phalanx with marked enhancement. The tumor had a high signal intensity on T2-weighted images. Local recurrences of this tumor are common after simple local excision but distant metastases are infrequent.

A painful left ring finger with pulp enlargement was diagnosed as Kaposi sarcoma with bone extension in a 63-year-old woman with long-standing AIDS and previous Kaposi sarcomas [899]. The clinical examination found moderate nail dystrophy associated with a purplish nodular lesion under the nail. Radiography revealed an osteolytic lesion of the distal phalanx. A T1-weighted MR image showed a hypodense tumor of the phalanx.

Florid reactive periostitis of the tubular bones of the hands and feet [900], also called fibroosseous pseudotumor of the digits [901, 902], is a benign lesion that may simulate osteosarcoma. This reactive lesion of the digits occurs in the soft tissue of middle-aged adults, also in the distal phalanx and subungually [902, 903]. An antecedent trauma appears to be present only in a minority of patients [904]. Enlargement of the distal phalanx and onycholysis may result from its insidious growth. Radiologically, well-defined calcified masses, often most dense at the periphery of the lesion, were present in 58%
of the patients [903] but initial plain radiographs may appear normal. A periosteal reaction was associated with the calcified swelling in 42% of patients. MRI reveals a benign-appearing mass with calcification [905]. Local surgical removal is the treatment of choice [903] but might be extremely difficult [906]. The lesion may, microscopically, resemble myositis ossificans [901], and the opinion is that myositis ossificans and fibroosseous pseudotumor represent the same pathological process [903, 904]. It is not clear whether “bizarre parosteal osteochondromatous proliferations of the tubular bones of hands and feet” are different from fibroosseous pseudotumors [907]. One case presenting as paronychia of the right thumb was described by Derrick et al. [908].

Epithelioid sarcoma

Epithelioid sarcoma is a sarcoma of unknown lineage that usually occurs in the soft tissues of young adults, but cases in children have also been reported [909, 910]. It is the most common soft tissue sarcoma of the wrist and hand [911] and may arise from the synovial membrane of the distal interphalangeal joint and cause “diffuse swelling” [912, 913], whereas others mimic a wart [914] or hard ganglion cysts. The tumor spreads to affect the dorsal aspect of the tip of the digit (Fig. 21.146a). Peripheral epithelioid sarcoma manifests as a slow-growing dermal nodule that might have been present for a long time, often misdiagnosed as a benign lesion [910, 911]. Although the majority of patients are otherwise asymptomatic, pain and tenderness are a complaint of some. A case was reported in a 12-year-old girl involving the distal left index finger as a tumoral lesion, which was ulcerated and painful [915]. Another case in an 11-year-old girl reported an erythematous nodule in the end phalanx of a finger, clinically resembling a ganglion [910]. An ulcerated tumor of the dorsum of the digit or its ventral aspect [916] may recur in the stump and eventually metastasize to lymph nodes and lungs. Metastases are found more often than in typical soft tissue sarcoma.

Although the majority of patients are otherwise asymptomatic, pain and tenderness are a complaint of some. A case was reported in a 12-year-old girl involving the distal left index finger as a tumoral lesion, which was ulcerated and painful [915]. Another case in an 11-year-old girl reported an erythematous nodule in the end phalanx of a finger, clinically resembling a ganglion [910]. An ulcerated tumor of the dorsum of the digit or its ventral aspect [916] may recur in the stump and eventually metastasize to lymph nodes and lungs. Metastases are found more often than in typical soft tissue sarcoma.

The differential diagnosis includes necrobiotic granuloma, giant cell tumor, malignant fibrous histiocytoma, squamous cell carcinoma, malignant melanoma, synovial sarcoma, and epithelioid hemangioendothelioma.

Histologically, the individual cells usually display marked eosinophilia and grow as nodular proliferations of plump, epithelial-appearing cells blending with fusiform cells [917] (Fig. 21.146b,c). The tumor usually has a strikingly granulomatous appearance with central necrosis. Immunohistochemistry is positive for the mesenchymal markers vimentin and CD34, and focally positive for the epithelial markers cytokeratin and EMA.

Local and plaque-like recurrences are common, but if the tumor is completely excised with wide margins, it does not recur locally.

Figure 21.146  (a) Epithelioid sarcoma. Courtesy of J. Revuz. (b,c) Histological changes showing many plump epithelial cells blending with fusiform cells.

Xanthomatous giant cell sarcoma

Hartert [918] described a case of xanthomatous giant cell sarcoma of the foot secondarily involving the fifth toe and its terminal phalanx.

Glomangiosarcoma

See the section on “Glomus tumor” in this chapter.
Leiomyosarcoma
Within the nail area, smooth muscle cells are found in two locations: arrector pili muscles and blood vessel walls. Superficial leiomyosarcoma is subdivided into cutaneous and subcutaneous forms with different clinical expression and prognosis [919]. The cutaneous form is assumed to derive from the arrector pili muscle and usually has a good prognosis because of its superficial location. This superficial type is probably responsible for leiomyosarcoma of the nail unit. The tumors are usually asymptomatic, solitary, firm nodules measuring 0.5–3 cm in diameter, but pain and tenderness have been recorded. Two adolescent cases involving the distal phalanx have been reported [733, 920], as has the case of an 81-year-old woman with a past history of local trauma who presented with a 2-year history of a painless nodule of the left index finger that had been increasing progressively in size [921]. Physical examination revealed an irregular, firm, and vegetating peri-ungual tumor of the left index finger that measured 2.5 cm in diameter. Another case concerned a 63-year-old man who had a non-traumatic avulsion of his right great toenail after a 3-week history of pain. Histopathological examination showed a neoplasm composed mainly of interlacing bundles of spindle cells with indistinct cell borders, eosinophilic cytoplasm, and pleomorphic nuclei. Immunohistological stains were positive for desmin and muscle-specific actin, but negative for S100, HMB 45, cytokeratin, carcinoembryonic and factor VIII-related antigens. The diagnosis was epithelioid leiomyosarcoma [922]. Microscopic differential diagnosis includes fibrosarcoma, malignant fibrous histiocytoma, and leiomyosarcoma. Cutaneous epithelioid leiomyosarcoma has negligible metastatic potential [923]. Primary treatment is surgical excision with narrow margins but emphasis on negative margins, unlike other sarcomas. Adjuvant radiotherapy or chemotherapy, or both, are of little if any benefit [920].

Fibrosarcoma
Fibrosarcoma is a malignant spindle cell tumor that exhibits fibroblastic differentiation without synthesis of an osseous or chondroid matrix. Fibrosarcoma may occur everywhere where fibrous connective tissue is found but is rare in hands and feet [924]. Fibrosarcoma of adults usually arises superficially as a hard, fixed, painful tumor but may present as a deep swelling, often reaching a large size with a tendency to invade the skin and neighboring tissues. The tumor may grow slowly over a period of many years and then demonstrate rapid growth, or may be rapidly invasive from the start. The ulcerating fibrosarcoma on the left middle finger of a 25-year-old man grew in a period of 5 months to a diameter of 10 cm [926]. Metastases to the lung and, less commonly, to regional nodes occur early. Amputation and adjuvant chemotherapy offers the best chance for cure.

Congenital infantile fibrosarcoma
Congenital infantile fibrosarcoma is a rare tumor that primarily develops in the soft tissue of distal extremities in children below the age of 5 years. Histologically, it is identical to classic fibrosarcoma of adults [927]. It is regarded as a tumor of borderline or low malignant potential [927] and presents as a rapidly expanding, dusky, firm swelling resembling hemangioma, lymphatic malformation, or a hemorrhagic vascular malformation. Two cases involving a whole finger of a neonate were reported [928, 929]. After resection, chemotherapy, or, rarely, radiotherapy the tumor uncommonly metastasizes, but local recurrence may occur.

Myxoinflammatory fibroblastic sarcoma
(Acral) myxoinflammatory fibroblastic sarcoma is a rare low-grade sarcoma, usually observed in the extremities of middle-aged patients. Seventy-five percent of cases present in the fingers and hand but ungual lesions have not been reported [930, 931]. Clinically the lesion is a painless, slowly growing, well-circumscribed tumor with lobules, has a yellowish color, and is sometimes mucoid [932]. Occasionally, areas of necrosis and hemorrhage are found. Microscopically, there are three main characteristics: a somewhat multinodular overall architecture with alternating densely cellular and myxoid hypocellular areas; a mixed inflammatory infiltrate; and bizarre giant and lipoblast-like cells. The tumor may recur after excision but metastases are rare.

Chondrosarcoma
While most cartilaginous tumors are benign, chondrosarcoma is the most common primary malignant bony tumor of the hand and can present at any age. About 50% of hand chondrosarcomas affect phalangeal bone, but involvement of the distal phalanx with its nail unit is rare, with few reported cases [933–936]. Pain and swelling are common symptoms [937–939]. In contrast, patients with benign cartilaginous tumors of these bones rarely have pain unless pathological fracture has occurred [940]. Initially, nail deformation may go unrecognized for months until sudden pain and aggressive digit swelling develop. A case of pincer nail development due to a subungual chondrosarcoma has also been published [934], and a 50-year-old woman had a 20-year history of severe nail clubbing before pain developed and the diagnosis of chondrosarcoma was made [935]. Trauma was assumed to be a precipitating factor for a chondrosarcoma of the distal phalanx in a 33-year-old woman [936].
Radiologically, a chondrosarcoma is a large and well-defined lesion with expanded bone contours and endosteal scalloping. Cortical destruction and extraosseous extension with tiny calcifications in clusters are indicative of active and more aggressive lesions [798]. On early radiographs, these patterns may be subtle and the diagnosis is difficult. MRI is helpful and shows abnormal patterns for a simple enchondroma. Some areas show a typical signal behavior of hyaline cartilage, but other areas present an unusual mottled enhancement. Phalangeal chondrosarcoma is resistant to chemotherapy and radiotherapy. It has been categorized as a neoplasm different from classical hand chondrosarcoma with respect to the minimal metastatic potential, but has a high risk of locally aggressive behavior [941]. Hence, surgical treatment is mainly indicated because of its locally destructive growth, although metastases have been reported [941, 942].

The risk of developing a chondrosarcoma from an enchondroma is estimated to be about 4% but is higher in individuals with Ollier or Maffucci syndrome, where the risk approaches 25% and 100%, respectively [800, 814]. Clinically, the presence of non-mechanical pain or night pain is cause for concern and further immediate investigation is indicated. The risk of malignant change in the multiple exostoses syndrome varies from 1% to 25% but there is no report of malignancy in the distal phalanx. A combination of squamous cell carcinoma and chondrosarcoma, the carcinosarcoma, has been reported as a painful exophytic mass on the tip of the middle finger of the right hand, involving the distal part of the nail bed [943]. A case of multiple subungual secondary chondrosarcoma has been reported [944].

Ewing sarcoma

Ewing sarcomas are tumors that are presumably derived from primitive neuroectodermal cells or from a mesenchymal stem cell. They can occur anywhere in the body, but are most common in the pelvis and proximal long tubular bones in patients younger than 20 years of age [945]. Ungual Ewing sarcoma is very rare, but impressive case reports exist, mostly presenting with pain and a fixed swelling of the digit [945]. Low-grade fever is common. Two out of the 377 cases of Ewing sarcoma described by Reinus et al. [946] were located on a distal phalanx. Radiography reveals an invasive soft tissue mass, and often an associated sclerotic reaction [946]. The first case reporting a Ewing sarcoma on a distal phalanx described a painless ulcerating swelling of the right thumb in a 12-year-old boy [947]. A case report in a 13-year-old girl described the lesion as a painful and diffusely tender, warm, cystic swelling of the tip of the finger [948]. It may also present with a painless swelling with ulceration of the tip of the digit, or with a slowly enlarging painful swelling of the distal phalanx with a subungual fleshy mass resembling granulation tissue [949]. A nail–patella syndrome associated with a Ewing sarcoma was published by Steens et al. in 2007 [950]. Although almost all cases of Ewing sarcoma were reported in minors, the tumor may also be found in adults up to the age of 62 [951], as was also illustrated by a 51-year-old man with a tumor that was initially adjacent to the nail of the right thumb [952]. Rapid and destructive growth occurred some years later when the patient presented with a 60 mm multinodular tumor involving the thumb tip, showing extensive areas of necrosis associated with bacterial infection. This rapid and destructive growth was also found in another adult patient, presenting with a 95 mm polypoid, necrotic mass on the first toe, with irregular edges, ulceration, and bleeding [953]. The radiological examination is highly abnormal in Ewing sarcoma, and biopsy provides the final piece to make the diagnosis. The combination of excision and postoperative adjuvant chemotherapy may have the best prognosis but radiotherapy is another treatment option [945].

Pseudotumors

Myxoid pseudocysts of the digits

Definition

Myxoid pseudocysts (MPC) are common and are called dorsal finger cysts, clear cysts, mucous cysts, myxoid cysts, joint ganglions, and many other names [80, 954].

Epidemiology

The exact incidence and prevalence are not known although it is estimated that women are affected more than twice as often as men [955].

Physiopathology

Whereas some authors regard MPC as degenerative lesions, others believe them to be traumatic or synovial cysts. Degenerative, “wear and tear” osteoarthritis, frequently with Heberden’s nodes, is present in almost all cases [956–960]. Kleinert et al. [961] reported a communication between these cysts and the joint and proposed that they were mucous cysts rather than a local soft tissue degeneration. They found that most occurred at an osteoarthritic spur on the distal interphalangeal joint, which allowed egress of joint fluids to fill and expand the cystic structure. Communication between cysts and the distal interphalangeal joint was revealed by MRI in 80% of subungual myxoid cysts [962] (Fig. 21.147).

Etiology

In two cases, the patient’s occupation has been incriminated as the cause of MPC by increasing the pressure within the joint with subsequent capsule rupture [963, 964].
After the patients stopped work several MPC spontaneously resolved or became smaller. The occurrence of digital myxoid cyst and epidermal inclusion cyst simultaneously at the same site might be caused by trauma [965].

**Clinical features**

MPC are typically found in the proximal nail fold of the fingers and rarely on toes; middle and index fingers and thumb are most frequently affected. MPC are usually solitary but multiple MPC may occur in the same individual, usually two or three [964, 966]. Location of the tumor at the corner of the cul-de-sac following subungual hematoma [967] is exceptional.

Clinical features depend upon their location in the nail apparatus. De Berker classified them into three subtypes [962, 968]:

- **Type A**: in this most common presentation, the MPC is located between the crease of the distal interphalangeal joint and the proximal nail fold. It mostly lies lateral to the midline and rarely exceeds 10 mm in diameter. It is usually asymptomatic, varying from soft to firm, cystic to fluctuant, and may be dimpled, dome shaped, or smooth surfaced (Fig. 21.148a). The skin over the lesion is often thinned and may rarely be verrucous or even ulcerate.

- **Type B**: the MPC is within the proximal nail fold and pressure on the underlying matrix produces a longitudinal grooving in the nail plate facing the MPC [966]. The groove may be smooth, meaning that the MPC is of constant size (Fig. 21.148b), or may vary in depth according to the fluctuating volume of the cyst (Fig. 21.149a). Spontaneous rupture and release of the content into the cul-de-sac beneath the proximal nail fold may suggest chronic paronychia (Fig. 21.149b) or present as dried material emerging in the longitudinal groove from under the cuticle, evoking a fibrokeratoma (Fig. 21.149c). Interestingly, transepidermal elimination of mucin with collections of mucin in an intraepidermal bulla was reported in one case [969].

- **Type C**: in some rare instances, the MPC may extend beneath the nail plate and is more difficult to recognize. The color of the lunula is red or blue [970], and only rarely is normal. This change in nail color was a striking and useful clinical sign in 25 of the 35 cases reported by de Berker [962]. Splitting and partial destruction of the nail can be seen in almost half of cases of subungual myxoid cyst (Fig. 21.148c) [962]. Subungual MPC may result in transverse overcurvature of the nail [962, 971, 972]. This takes the form of a pincer nail if the cyst is central, or lateral ingrowing if the cyst lies eccentrically [962, 966, 968]. Disruption of the nail is an exception.

Complications of MPC are rare. Purulent drainage due to infection and development of septic arthritis of the distal interphalangeal joint have been reported [973].

**Differential diagnosis**

The main differential diagnosis is Heberden’s nodes for type A, fibrokeratoma for subtype B, and submatrical tumors of any origin for type C.
Diagnosis
In most cases the diagnosis of MPC can be made clinically. Pricking with a needle will release a thick, clear, gelatinous fluid (Fig. 21.150).

Medical imaging
Transillumination confirms the cystic nature of MPC. Polarized dermoscopy reveals vascular patterns (arborizing vascular patterns, dotted vessels, linear vessels and polymorphous vessels, red-purple lacunas) in more than half of cases [974]. Osteoarthritis of the distal interphalangeal joint is noted in 70% of cases on radiographs [975]. MRI [976] is rarely indicated. The MR appearance is specific with thin, regular walls, a low signal on T1-weighted images, and very high signal on T2-weighted images. Intracystic septa are best seen on T2-weighted images. A pedicle connecting the cyst and the distal interphalangeal joint is visible in most cases with MRI (Fig. 21.147). In all cases, the pedicle is lateral, beneath the insertion of the extensor digitorum tendon on the base of the distal phalanx. On MRI, mucoid cysts extend into the nail bed in 30% of cases [975]). When the cyst is large, an erosion of the cortex of the underlying phalanx may occur in the confined space of the nail bed.

Pathology
Histopathology reveals the pseudocystic character (Fig. 21.151). The structure is essentially myxomatous with interspersed fibroblasts. Quite often, true myxomatous areas are seen in the vicinity of cystic-appearing cavities so that different aspects may be manifest as the
lesion ages [977]: fresh lesions are myxomatous, mature lesions cystic. Areas of myxomatous degeneration may merge to form a multilocular pseudocyst. In the cavities, a jelly-like substance is found which stains positively for hyaluronic acid. Cavities without a synovial lining are located in an ill-defined fibrous capsule. Goldman et al. [978] found a mesothelial-like lining only in the stalk connecting the pseudocyst with the distal interphalangeal joint. Electron microscopy does not show a synovial lining of the pseudocyst but myofibroblasts, which are also abundant in the mucopolysaccharide-like stroma. Immunohistochemically, these cells mainly stain for vimentin, but some are faintly desmin positive [979].

Management

Numerous treatments have been recommended for MPC. Their aim is to obliterate the leakage from the joint by inducing fibrosis around the capsule. Spontaneous regression has been documented but is reportedly rare [964], justifying symptomatic treatment. For fearful and elderly persons, a non-aggressive approach should be proposed: multiple needlings and expression of contents [980], associated with compressive dressings, were shown to have a cure rate of 72% [980]. Cryotherapy of MPC type A followed by compressive dressings resulted in a cure rate of 56–86% [981–983]. Two freeze/thaw cycles were carried out, each freeze time being 30 s after the ice field had formed, the intervening thaw times being at least 4 min. Injection of sclerosant is favoured by some authors: after the cyst has been pierced and its jelly-like material expressed, 0.10–0.20 mL is injected, painlessly, to gently refill the cyst to its previous size. One single procedure may be enough. Second or third procedures can be performed at 1-month intervals. Recent publications used intraleisional sodium tetradecyl sulfate injection [985] and 3% polidocanol [984], both with 80% success. Even if largely successful, use of this technique should be limited as it may cause severe unexpected permanent nail dystrophy (Fig. 21.152a,b) and joint stiffness. CO₂ laser was tried in a small series with a 100% cure rate [986, 987] and more recently infrared coagulation was proposed with a high success rate [988, 989]. None of these techniques has been able to attain the constant high rate of success achieved with surgery. Hand surgeons usually remove the osteophytes and “clean” the joint capsule [956, 957, 959, 990]; identical success rates of up to 90% [957] were found with osteophytectomy with and without removal of the cystic lesion. This leads to very good results (Fig. 21.153) but this aggressive surgery may result in restriction of joint mobility (up to 25%) and postoperative recovery is long and painful for the patients [959]. If the MPC is located very distally on the proximal nail fold, an “en bloc” resection of the lesion as for chronic paronychia is recommended [991] (Fig. 21.154).

Methylene-blue guided surgery for ligature of the leak of joint fluid is a very elegant, quick, and effective technique as it provides a very high success rate. This procedure is also very comfortable for the patient. Kleinert et al. [961] recommend careful extirpation of the lesion. A tiny drop of methylene blue solution, mixed with fresh hydrogen peroxide, is injected into the distal interphalangeal joint at the volar joint crease. The blue color clearly identifies the pedicle connecting the joint to the cyst and the cyst itself which may look like a subcutaneous tenoarthrosynovial “hernia” [879]. This procedure sometimes also reveals occult satellite cysts. The lesion is meticulously dissected from the surrounding soft tissue and the pedicle traced to the joint capsule and resected. Dumb-bell extension of cysts to each side of the extensor tendon is easily dissected by hyperextending the joint [992].

De Berker and Lawrence modified this procedure, removing the need for excision. A maximum of 0.4 mL of methylene blue solution is injected into the distal interphalangeal joint at the volar joint crease. A skin flap is designed around the cyst and raised to identify the dye-filled communication between joint and cyst. The communication is ligated and the flap replaced with no tissue excision [993] (Fig. 21.155a–c). The cure rate is 94% on the fingers but reaches only 57% in the toes, probably because in this location the pressure of fluid escaping from the joint is increased by the weight of the standing position.

Proximal nail fold flap dissection was introduced by Lawrence in 2005 [994]: the leakage point in the dorsal capsule is sealed in the healing process that occurs after a flap is raised and re-sited. The flap must be designed to include the undersurface of the cyst and the tissues between the distal interphalangeal joint and the cyst.
One series reported a success rate of around 60% [995]. This procedure is especially recommended for toes. A transposition flap was also described to obliterate the leakage (Fig. 21.156a) [996]. Another surgical technique, based on the excision of the digital mucous cyst and reconstruction using self-grafting from the overlying skin lesion, has recently been reported (Fig. 21.156b) [997].

Complications following resection of MPC are mainly joint stiffness, loss of residual motion, persistent swelling, pain, deviation of the distal interphalangeal joint, and infection [961].

**Pretibial myxedema**

Pink or flesh-colored mucinous plaques may involve the dorsal aspect of the foot and exceptionally the toes, partially hiding the nails (Fig. 21.157). These firm and non-pitting plaques generally are present in patients with severe Graves ophthalmopathy [998]. The atypical localization may correlate with a Koebner phenomenon [999]. Treatment of Graves disease is generally insufficient to resolve the cutaneous problems. Topical corticosteroid therapy generally results in rapid improvement of recent lesions.

**Primary osteoma cutis**

Burgdorf and Nasemann [1000] used the term “primary osteoma” of the distal extremities to identify osteomas in...
six patients presenting with firm nail bed tumors in five toes and one finger. Bone alone was found in four cases and ossifying cartilage in two. Blatière et al. [1001] reported on a 16-year-old girl presenting with a longitudinal hemorrhagic streak associated with distal splitting of her left third fingernail (Fig. 21.158a). Histology of the tiny tumor found within the nail matrix revealed an osteoma cutis (Fig. 21.158b).

Subungual calcifications
Primary subungual calcifications in the normal nail bed of the digits are occasionally seen in the elderly, especially women [1002] (Fig. 21.159). The frequency decreases from the second to the fifth digit. In about 10% of cases, the subungual calcifications of the fingers are combined with subungual calcifications of the toes [1003]. Soft tissue calcification at the margin of the distal phalanges of the fingers occurs in 7% of normal adults [1004]. In the normal toenail bed, it begins in women during their 30s and reaches a prevalence of 47% in their 80s.
These calcifications appear in men two decades later and attain a prevalence of only 4% in old age. The first toe is involved three times as often as the fifth toe [1005]. Secondary subungual calcification occurs occasionally after trauma and in psoriasis [1002]. The soft tissue calcification at the margin of the tuberosity of the distal phalanx of fingers results from mechanical injury of the collagen fibers close to their insertion into the bone [1003, 1005]. Multiple subungual calcifications can also be seen in cases of calcified subungual epidermoid inclusions [199]. These calcifications caused progressive deformity of the right great toenail in a 73-year-old woman. The nail showed diffuse nail plate thickening and yellow discoloration. There was distal onycholysis,

---

Figure 21.158 (a) Primary osteoma cutis in the nail matrix. (b) Histological changes of case shown in (a).

Figure 21.159 (a) Subungual calcification of the distal nail bed and the hyponychium. Courtesy of C. Beylot. (b) Radiograph revealing calcifications in case shown in (a). (c) Calcification involving sequelae of hemangioma case shown in (a). Courtesy of C. Perrin.
particularly in the midline of the plate, and the thickened lateral plate formed a central cavitation, suggesting mid-nail bed disease. Histopathology showed cyst formation in the dermis composed of a basal layer, spinous layer, and compact keratin, without a granular layer. Scattered epidermoid inclusions were calcified.

Cutaneous calculi

Winer [1006] first recognized “solitary congenital nodular calcification of the skin” as a distinct entity. This rare condition presents from birth as slowly enlarging, hard, yellowish-white, warty nodules at the side of a finger or a toenail (Fig. 21.160). In fact, they are not always solitary and frequently are not congenital [1007]. The distal aspect of the involved digit may appear erythematous, with a solid, chalky white, well-circumscribed lesion that is not tender to palpation. Radiographs demonstrate a radiopaque mass, consisting of multiple calcified fragments located adjacent to the distal phalanx [1008] in a subepidermal location. Cutaneous calculi may be difficult to distinguish from calcinosis circumspecta.

Oxalate granuloma

Several pink, lightly keratotic, tender subungual nodules affecting two digits combined with multiple, tiny, tender, yellow-tan papules on several fingertips were reported in a 46-year-old white man with chronic renal failure treated by hemodialysis for 20 years (Fig. 21.161a). Biopsy specimen of a subungual nodule showed a corymbiform arrangement of calcium oxalate crystals surrounded by foreign body granulomas in the dermis [1009] (Fig. 21.161b,c).

Figure 21.160 Congenital calcification involving lateral nail fold of the toe. Courtesy of P. Souteyrand.

Figure 21.161 (a) Oxalate granuloma. Courtesy of B. Sina. (b) Oxalate granuloma: many crystals surrounded by granuloma cells (from (a)). (c) Oxalate granuloma: photo of polarization microscopy showing the crystals within the dermis (from (a)).
Gout
See Chapter 15.

Histiocytic, lymphomatous, and metastatic processes

Histiocytic processes

Xanthoma
Keller [1010] reported a case of hypercholesterolemic xanthomatosis in a 61-year-old woman exhibiting pseudo-Koenen tumors periungually in the second and third toes.

Verruciform xanthoma
Verruciform xanthoma is a rare skin condition characterized histologically by uniform epithelial acanthosis and foam cells within elongated dermal papillae. There is no atypia. Verruciform xanthoma also occurs, rarely, as a secondary reaction in lesions with marked epidermal hyperplasia, such as epidermal nevus and inflammatory linear verrucous epidermal nevus (ILVEN), and is also seen in congenital hemidysemblyplasia with ichthyosiform nevus and limb defects (CHILD) syndrome, a rare X-linked hereditary disorder [182, 183, 1011]. Hashimoto et al. [182] reported a 3-year-old girl with linear and verrucous lesions extending on her hands, fingers, and periungual skin. The cooccurrence with other symptoms led to the diagnosis of CHILD syndrome. “Raspberry-like,” huge, verrucous tumors on the distal phalanx of the finger have been described in two cases of CHILD syndrome by Bittar and Happle [1011]. Fedda et al. [183] described an impressive case of a 17-year-old girl with CHILD syndrome, presenting with an exophytic slow-growing mass on her right foot since the age of 10.

Chyu et al. [1012] reported a 36-year-old black woman with verruciform xanthoma on the right first toe of a lymphedematous leg. This was a recurrent yellow-tan tumor, present for 18 months and slowly increasing in size to form a 2 cm yellowish, fungating, verrucous nodule involving the proximal nail fold. It was asymptomatic until its size interfered with the fit of her shoe.

A patient with multiple verruciform xanthomas [1013] presented with a fingernail which was severely dystrophic and for the most part absent. The remaining part of the lesion measured 1 × 1.5 cm and appeared verrucous, with some crusted exudate that encompassed the nail bed.

Langerhans cell histiocytosis
Langerhans cell histiocytosis (LCH) comprises a group of disorders characterized by clonal proliferation of Langerhans cells. Most LCH patients have single-system disease, which commonly involves bone, skin, or lymph nodes. Involvement of the fingernails or toenails is rare [1014] but occasionally may precede multiorgan LCH in infants by many months [1014, 1015]. Multifocal restricted single-system LCH is often diagnosed in children aged between 2 and 5 years. The histology of nail unit lesions is similar to that of cutaneous lesions, comprising atypical Langerhans cells [1014]. Extensive asymptomatic subungual hyperkeratosis, involving several fingernails and toenails, is the main sign of nail involvement. Other signs are hemorrhages, pustules, longitudinal grooving, pitting, paronychia of the proximal or lateral nail folds, cheesy yellowish discharge from nail beds, and onycholysis up to onychomadesis (Fig. 21.162a–d) [1014, 1016–1018]. Linear splinter hemorrhages of the nail were the only nail sign in a 2½-year-old boy with LCH [1019]. The significance of nail changes as an independent (poor) prognostic indicator is controversial; nail changes in LCH mostly occur in patients with multisystem disease, which is known to be significantly related to mortality. In the scarce published

Figure 21.162 (a–c) Nail involvement in Langerhans cell histiocytosis. Courtesy of D. de Berker. (d) Skin involvement in the same patient.
cases in which nail changes were not associated with multisystem disease, the prognosis was excellent [1018, 1020]. Patients at risk include those with systemic involvement and young age (<2 years); these patients have a high mortality rate, ranging up to 66% [1021].

Non-Langerhans cell histiocytoses (juvenile xanthogranuloma, multicentric reticulohistiocytosis)

The non-Langerhans cell (LCH) histiocytoses are a diverse group of disorders characterized by the accumulation of histiocytes that do not meet the phenotypic criteria for LCH. Many variants of these diseases have been described.

Juvenile xanthogranuloma (JXG) is the most common form of non-Langerhans cell histiocytosis. It is a benign, self-limited, histiocytic proliferative disorder that is most frequently seen in children. The head, neck, and trunk are the most frequent locations but lesions of the nail unit have been described [1022–1026]. All patients described with nail involvement in JXG were under 3 years of age, the youngest being 25 days old [1027], and presented with a wide range of clinical signs: lesions from the proximal nail fold covering part of a finger and resulting in a hyperkeratotic cuticle, or resulting in longitudinal depressions of the nail plate indicating nail matrix compression by the lesion [1025, 1026] (Fig. 21.163a,b). Lesions arising from the nail bed may lift the nail plate and result in onychogryphosis [1022, 1023]. In Frumkin et al’s case [1023], the whole nail bed and the matrix were seen to be occupied by a round, yellow, soft tumor, 6 mm in diameter. Histology revealed lipidized macrophages intermingled with lymphocytes, eosinophils, foam cells, and giant cells of the foreign body and Touton type. These latter exhibited the characteristic “wreath” of nuclei. Histological analysis is necessary for the diagnosis, especially to differentiate JXG from Langerhans cell granuloma. JXG regresses spontaneously within 2–6 years, often leaving residual atrophy or discoloration. Surgical removal may be indicated to prevent permanent dystrophy but periodic follow-up may be sufficient to monitor evolution in order to prevent excessive growth of the lesion with possible definitive nail matrix damage [1026]. Although JXG is a benign condition and most patients only have a solitary lesion, it is important to rule out the presence of other possible skin, mucosal, or extracutaneous lesions in many organ systems [1022]. In particular, intraocular involvement occurs relatively frequently. The possible association with NF type 1 should also be considered.

Nail symptoms may also occur in other variants of non-LCH. Patel et al. [1028] reported a 57-year-old woman presenting with a 14-year history of multiple pale-yellow, firm, well-demarcated nodules on the hand. Most of the lesions were concentrated around the interphalangeal joints, on both the extensor and flexural surfaces. Based on the abundance of histiocytes, the absence of Langerhans cells, CD68 positivity, and S100 negativity, the patient was considered to have a form of non-LCH. These clinicopathological findings were thought not to fit with recognized variants of non-LCH. Clinically this case resembled multicentric reticulohistiocytosis (MR) which most often presents in older women as cutaneous nodules on the face and hands, with a symmetrical erosive arthritis; there is a significant association with malignancy [1029]. Many small, smooth, and shiny erythematous papules along the nail folds may form the “coral bead sign” [1030] and represent a typical sign. The lesions may be pruritic and be disseminated over the dorsal areas of hands and fingers, especially around the joints [1031]. The combination of nodules on the distal phalanges along with coalescing nodules in the periungual area with a “beaded string” appearance should raise suspicion [1032, 1033]. The disease is associated with an underlying malignancy in 15–28% and a coexisting autoimmune disorder in 6–17%. The disease typically remits within 5–10 years.

Multicentric reticulohistiocytosis
See Chapter 15.

Lymphoma
See Chapter 15.

Metastases

Metastases to the fingertip or nail region (Fig. 21.164) are quite rare (about 150 cases reported [1034]) and are often initially misdiagnosed as acute infection in and around the nail apparatus and treated as such by antibiotics or incisions [1035, 1036]. Acrometastases are usually associated with a high tumor burden and poor prognosis. The mean survival for patients with presentation of a metastatic
hand lesion is merely 6 months [1037]. Metastases can be divided into osseous and cutaneous. These lesions relatively often are the first manifestation of an internal neoplasm [1035, 1038, 1039]. Most metastatic tumors primarily affect the bone with subsequent spread to soft tissues. Primary soft tissue metastases of the distal digit may secondarily involve the underlying bone. Subungual metastases may involve either a single digit of the hand or foot, or multiple digits of the same hand or foot, and/or both hands or feet [1040, 1041].

The symptoms and signs of metastases are very variable and include dusky red, painful or painless swelling (Fig. 21.165a), expansile pulsation, pseudoclubbing [1034, 1042], nail dystrophy, and changes simulating acute or chronic paronychia [1040], a finger infection such as whitlow or osteomyelitis [1043], and even benign lesions such as glomus tumor [1044] and early rheumatoid arthritis [1045]. A clinical picture of necrotizing vasculitis involving the nail area was mimicked by metastatic hypopharyngeal carcinoma [1046] and by pulmonary squamous cell carcinoma [1047]. Nail metastasis should be suspected when there is a discrepancy between clinical signs and degree of pain, especially in the absence of injury or infection [1038]. With time, a reddish-purple nodule in the distal nail bed and hyponychial region may become ulcerated.

Figure 21.164 Metastasis of a colon carcinoma, presenting with painful clubbing and expanding in the lateral nail fold.

(a) (b) (c)

Figure 21.165 (a) Metastasis: lung carcinoma. (b) Radiological image. Note the preservation of the joint. (c) Metastasis from bronchial carcinoma.
Radiographs usually show an osteolytic focus that may resemble spina ventosa or osteitis. Distal phalangeal metastases usually do not cross the articular surface (Fig. 21.165b). In fact, they characteristically preserve a thin margin of subchondral cortical bone and, sometimes, a blown-out cortical shell [505]. Fine needle aspiration cytology or, better, incisional biopsy is necessary to classify the tumor and exclude a primary bone growth but even this may fail to reveal the true nature of the primary lesion.

Bronchial carcinoma represents 41% of phalangeal metastases (Fig. 21.165c) [1035]. The other primary tumors include breast (9%), kidney (11%), liver, colon [1048], rectum [1049], hypopharynx, larynx, oral cavity, and parotid gland carcinoma [1050], seminoma [1051], choriocarcinoma [1052], endometrial carcinoma [1053], melanoma [1054-1056], osteosarcoma [1040], neuroblastoma, plasmacytoma, chondrosarcoma, epithelioid angiosarcoma [1057], also non-melanoma skin cancer and adrenal gland carcinoma.

Melanocytic lesions

Melanocytes in the nail unit

Melanocytes are present in the nail matrix and nail bed although they usually remain functionally inactive in white people. When they become active and produce melanin in amounts that can no longer be degraded by the keratinocytes of the matrix, melanin will continuously be enclosed in the growing nail plate, giving rise to a longitudinal light brown to black band (Figs 21.166, 21.167). A relatively rapid enlargement of a subungual pigmented lesion may be seen as a stripe that is wider in its proximal part; estimation of the nail growth rate and measurement of the difference in width proximally and distally allows an exact calculation of the growth of the pigment-producing lesion. Except for “subungual linear keratotic melanonychia” [158], pigmented lesions in the nail bed usually do not cause a longitudinal melanonychia but shine through the nail as a grayish to brown or blue or black spot.

Longitudinal melanonychia (melanonychia striata longitudinalis)

Longitudinal melanonychia (LM) is characterized by a tan, brown, or black longitudinal streak within the nail plate (Fig. 21.168). LM results from increased melanin deposition in the nail plate. This deposition may result from greater melanin synthesis by normally non-functional matrix melanocytes (Figs 21.169, 21.170) or from an increase in the total number of matrix melanocytes that synthesize melanin; in either instance, melanocytes may be normal or abnormal.

Perrin et al. [1058] have demonstrated that proximal nail melanocytes contain premelanosomes and melanosomes I and II, but not the “mature” melanosomal compartment; therefore the dormant melanocytes are predominant. In the distal matrix, the same authors observed an active melanin synthesis compartment.
Tumors of the Nail Apparatus and Adjacent Tissues

(i.e. functionally differentiated), associated with a dormant melanocyte compartment. In contrast to common belief, LM originates more often in the distal matrix, not secondary to the larger melanocyte density but because only the distal matrix contains melanocytes with active melanin synthesis. This is a fortunate circumstance because permanent nail plate deformity is less common when surgery is performed in the distal rather than in the proximal matrix. The more proximal the origin, the more superficial is the melanin within the nail plate (Fig. 21.167). It is possible to identify the site of origin of pigmentation in LM within the matrix by staining a nail plate clipping with Fontana–Masson's staining (Fig. 21.171). Dermoscopy of the free edge of the nail plate can also provide the same information [1059].

When distal matrix origin seems likely, the cuticle can sometimes be retracted proximally to confirm the distal origin of LM without incision of the proximal nail fold. LM is common in darkly pigmented persons. It occurs in 77% of African-Americans over 20 years of age and in almost 100% who are older than 50 years; the thumbs and index fingers are most frequently involved. LM occurs in 10–20% of Japanese people; the thumbs and index and middle fingers are most frequently involved in this group. LM is also common in Hispanics and other dark-skinned groups. Among white people, LM is unusual.

The distribution of LM between digits coincides with relative digital use; LM is most common in frequently used fingers. The thumb, always used in grasping, is the digit that most often demonstrates LM. The index, middle, fourth, and fifth fingers are employed with diminishing frequency for grasping objects and demonstrate a correspondingly lower incidence of LM. More frequently used digits are also subject to greater trauma. Several authors have implicated trauma in the pathogenesis of subungual melanoma (SM) [1060–1062]. The distribution of LM and SM is remarkably similar. SM develops slightly more often on the hand than on the foot.
Forty-five percent to 60% of SM arises on the hand, 40–55% on the foot [569]. On the foot, SM usually occurs in the great toe. Is the incidence of SM higher in the thumb and great toe because each digit is subject to greater trauma, because LM, which commonly occurs on the thumb (and presumably the great toe), is a precursor of SM, or because the thumb and great toe occupy relatively large surface areas and afford greater opportunity for SM to develop?

To distinguish the small number of patients with SM from, by far, the larger group of patients with non-malignant LM is difficult. Both are alike in several ways. In the hand, each arises most often in the thumb, index finger, or both. LM has been reported to precede the onset of SM and may be an early sign of SM. Both are more common in dark-skinned persons.

In a Japanese study, 31% of SM started as LM and became ulcerated or painful several years later [1063]. In a Belgian study, six of 10 white patients with SM described as their first sign a longitudinal pigmented band of their nail [1064]. Other authors have reported similar findings.

Approximately 1–3% of malignant melanomas in white persons are SM [1065, 1066]. In Japanese persons, the proportion of SM was similar to that in white persons in two studies [1067, 1068] but higher, 10%, in a third one [1069], and 30% in that of Saida and Ohshima [1070]. In African-Americans, the proportion of SM was higher and varied from 15% to 20% [1070]. A study from Cape Town, RSA, of 20 SM, revealed seven white and 13 black patients [1071]. The proportion among Chinese people, 17%, was similar to that in African-Americans. The highest proportion of 33% was seen in a small study of American Indians [1071]. In general, when melanoma occurs in dark-skinned persons, a higher percentage of melanomas is likely to arise in the nail apparatus [1071], palm, or sole, whereas in light-skinned persons a lower percentage is likely to arise in the nail apparatus (Fig. 21.172).

A thorough history and physical examination should enable the various exogenous causes of a single band of LM to be distinguished. The most common pigmented lesion is subungual hematoma, which is easily distinguished from LM. It usually migrates distally and its proximal margin is gently curved in one transverse axis. If the nail plate is notched with a scalpel at the proximal margin...
of the spot, distal migration of the hematoma can be accurately measured as the nail plate grows (Fig. 21.173). Non-migratory hematomas and foreign bodies, however, do not follow this rule and require more extensive evaluation. Silver nitrate staining may sometimes be linear. It too grows out. Histopathology shows jet-black granules in the superficial layers of the nail plate [1072].

**Periungual pigmentation (Hutchinson’s sign)**

Periungual spread of pigmentation to the proximal and lateral nail folds as well as to the tip of a single digit is called Hutchinson’s sign [1073] and corresponds to the radial growth phase of SM. It is, therefore, the most important indicator of SM. When this sign is present, SM is the presumptive diagnosis (Fig. 21.174). This sign, however, particularly when subtle, is not absolutely pathognomonic for SM. Moreover, its biopsy is often not sufficient to accurately diagnose SM and must not be performed.

An illusory (pseudo) Hutchinson sign is produced when the pigmentation is visible through the translucent cuticle: LM that is dark brown simulates pigmentation of the overlying cuticle and proximal nail fold. The pigmentation is visible because of the relative transparency of the cuticle and proximal nail fold and not because of melanin deposition within these tissues (pseudo-Hutchinson’s sign). This can be identified by careful inspection. In good lighting, it is usually possible to establish whether pigment is present within the periungual tissues or beneath them in the underlying nail plate.

**Figure 21.173** (a) Subungual hematoma. (b,c) Subungual hematoma: notching of the proximal and distal margin of the lesion confirms its distal movement.

**Figure 21.174** (a–c) Melanoma: Hutchinson’s sign. (d) Melanoma: Hutchinson’s sign. Nail disappearance. (e) Non-melanoma: Hutchinson’s sign in congenital nevus.
As “benign,” “non-malignant,” and variants of Hutchinson’s sign occur in the absence of SM [1081] we now prefer to use the term “non-melanoma Hutchinson’s sign.” Each variant is characterized by periungual hyperpigmentation occurring in association with LM. Each represents a potentially misleading clue to the diagnosis of SM. The variants do not negate the importance of Hutchinson’s sign. Rather, they oblige the clinician to consider diagnostic possibilities other than SM. Likewise, the absence of periungual pigmentation does not preclude the diagnosis of SM. The clinician must carefully evaluate the individual patient for clues to the diagnosis of SM.

In addition to a detailed history of the present illness, careful clinical examination of the lesion, general physical examination, the history of the patient including drug ingestion, past treatments, hobbies, and illnesses, family history, racial origin, and general appearance must be evaluated. If the diagnosis of SM seems likely, an adequate biopsy of the involved nail unit is performed. In this manner, the pathologist is able to examine the tissue sufficiently to confirm or rule out SM. The relevance of Hutchinson’s sign to the diagnosis of SM has withstood the test of time. If the possibility of non-melanoma Hutchinson’s variants is kept in mind, the clinician is less likely to overdiagnose this important malignancy and more likely to address the problem with confidence and precision (Table 21.9).

### Table 21.9 Pigmented nail associated with non-melanoma Hutchinson’s sign.

<table>
<thead>
<tr>
<th>Condition</th>
<th>Clinical features</th>
</tr>
</thead>
<tbody>
<tr>
<td>Illusory pigmentation [1088]</td>
<td>Dark color traverses the transparent cuticle and thin nail fold</td>
</tr>
<tr>
<td>Ethnic pigmentation</td>
<td>Pigmentation of proximal nail fold in dark-skinned persons; lateral nail folds not involved; longitudinal melanonychia not present; often exaggerated in thumbs</td>
</tr>
<tr>
<td>Nail unit and mucous membrane pigmentation</td>
<td>Laugier syndrome [1074, 1089]</td>
</tr>
<tr>
<td></td>
<td>Peutz–Jeghers syndrome [1090]</td>
</tr>
<tr>
<td></td>
<td>Macular pigmentation of lips, mouth, and genitalia: one or several involved</td>
</tr>
<tr>
<td></td>
<td>Hyperpigmentation of fingers and toes; macular pigmentation of buccal mucosa and lips</td>
</tr>
<tr>
<td>Non-melanoma unit cancer</td>
<td>Bowen disease [269, 1091, 1092]</td>
</tr>
<tr>
<td></td>
<td>Basal cell carcinoma [1093]</td>
</tr>
<tr>
<td></td>
<td>Epidermodysplasia verruciformis [1094]</td>
</tr>
<tr>
<td></td>
<td>Mono- or polydactylous</td>
</tr>
<tr>
<td></td>
<td>Monodactylous</td>
</tr>
<tr>
<td></td>
<td>Monodactylous</td>
</tr>
<tr>
<td>Benign tumors of the nail unit</td>
<td>Onychomatricoma [229]</td>
</tr>
<tr>
<td></td>
<td>Superficial acral fibromyxoma [888]</td>
</tr>
<tr>
<td></td>
<td>Monodactylous</td>
</tr>
</tbody>
</table>

Periungual spread of pigmentation without SM may occur:

- In Laugier–Hunziker–Baran syndrome (Fig. 21.169) [1074, 1075], a disorder recognizable by the association of LM with macular pigmentation of the lips and mouth [1072, 1076–1078] as well as the genital [1079] and esophageal mucosa [1080]. This condition may also demonstrate isolated nail involvement [1077, 1081].
- In congenital nevus of the nail region [1082] and periungual recurrence of pigmentation after nail surgery for a nevus [1083].
- After radiotherapy for finger dermatitis [1084].
- As pigmented bands and periungual hyperpigmentation resulting from malnutrition [1085] and some drugs.
- LM in association with minocycline therapy.
- In acral pigmentation in Peutz–Jeghers syndrome.
- Along with pigmentation of the distal pulp in patients with AIDS even before the institution of systemic treatment [1086].
- In nevoid nail area melanosis and nail matrix nevus in children that may represent spontaneous regression [1087].
- After silver nitrate treatment of granulation tissue that causes a black halo which is easily distinguished from a Hutchinson melanotic whitlow.
Besides Hutchinson’s sign, other clues to the diagnosis of SM can be important [1115]. The clinician should be suspicious when LM (Table 21.10):

- begins in a single digit of a person during the third to sixth decades of life or later; however, melanonychia due to SM has even been observed in children (see the section on “Nail melanoma in childhood”) though the diagnosis in most published cases is debatable
- develops abruptly in a previously normal nail plate
- becomes suddenly darker or wider (Fig. 21.168)
- occurs in the thumb, index finger, or great toe
- occurs singly in the digit of a dark-skinned patient, particularly if the thumb or great toe is affected
- demonstrates blurred, rather than sharp, lateral borders
- has a triangular shape

**Table 21.9** (Continued)

<table>
<thead>
<tr>
<th>Condition</th>
<th>Clinical features</th>
</tr>
</thead>
<tbody>
<tr>
<td>Congenital nevus [1095]</td>
<td>Pigment recurrence after biopsy</td>
</tr>
<tr>
<td>Acquired nevus [1096]</td>
<td>Monodactylous</td>
</tr>
<tr>
<td>Pigmentation following excision of nevi [1097]</td>
<td>Monodactylous</td>
</tr>
<tr>
<td>Subungual Spitz nevus [1098]</td>
<td>Monodactylous</td>
</tr>
<tr>
<td>Regressing nevoid melanosis in childhood [1087]</td>
<td>Initial increase in dyschromia followed by its subsequent regression</td>
</tr>
</tbody>
</table>

**Table 21.10** Correspondence between clinical warning signs of subungual and cutaneous melanoma [1118].

<table>
<thead>
<tr>
<th>Subungual melanoma</th>
<th>Cutaneous melanoma</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Anatomical criteria</strong></td>
<td>ABCD/Glasgow</td>
</tr>
<tr>
<td>Hutchinson’s sign</td>
<td>B/D</td>
</tr>
<tr>
<td>Nail dystrophy</td>
<td>E</td>
</tr>
<tr>
<td>Pigment full length</td>
<td>Beware</td>
</tr>
<tr>
<td><strong>Melanocytic criteria</strong></td>
<td></td>
</tr>
<tr>
<td>&gt;6 mm diameter</td>
<td>D</td>
</tr>
<tr>
<td>Variegated color</td>
<td>C</td>
</tr>
<tr>
<td>Blurred edges</td>
<td>A/B</td>
</tr>
<tr>
<td>Change or abrupt onset</td>
<td>Glasgow 1–3</td>
</tr>
</tbody>
</table>

ABCD/Glasgow differs from ABC rule for clinical detection of subungual melanoma [1119].
occurs in a person who gives a history of malignant melanoma
occurs in a person in whom the risk for melanoma is increased (e.g. dysplastic nevus syndrome) [1116] (Fig. 21.175)
is accompanied by nail dystrophy, such as partial nail destruction or disappearance.

Other signs are noteworthy, but not necessarily helpful, in establishing the likelihood of malignancy.

- Although amelanotic SM has been reported (Fig. 21.176) [1117], lightly pigmented bands of LM rarely represent SM, but do exist (Fig. 21.172); the pathologist may have difficulty even visualizing the melanin and melanocytes that constitute light-banded LM. We have seen two patients with pigmented nail bed melanoma without nail plate pigmentation.
- Darker shades of brown do not necessarily represent SM because nevi and melanoma may manifest identical shades of brown. In white people, black bands may be an important clue to SM; in African-Americans, however, “jet-black” bands are not unusual. Theoretically, color variegation suggests SM; however, variegation is common in persons with multiple “benign” LM.
- Theoretically, wide bands suggest SM; the critical width that signifies SM has yet to be established, although a width of >5 mm is usually critical.
- Bands that do not extend distally to the free edge of the nail are unlikely to represent SM because they do not take their origin from the nail matrix. However, they may represent metastatic melanoma or LM arising from the nail bed (see the section on “Melanoma metastasis”).

The management of black patients with pigmented bands can be difficult. Although multiple nails demonstrate LM, there may be substantial variability in the color and width of bands within a single nail plate and among different nails in the same patient. Whether LM in a thumb or great toe represents SM or racial variation is not necessarily easy to determine by history and inspection alone. Change in the morphology of LM, in particular widening and darkening, is the most important clue to the possibility of SM in these patients. A streak that is wider proximally than distally represents growth of the lesion in the matrix.

Multiple bands of LM are usually not neoplastic in origin although bilateral SM of the great toes has been observed once [1120]. A drug history and complete
general review to rule out relevant systemic disorders and a thorough examination of the skin and nails to exclude nail infection and associated cutaneous disorders may reveal the underlying cause of multiple LM.

However, despite meticulous evaluation, the etiology of LM remains obscure, and biopsy becomes necessary to avoid pitfalls [1121]. There is no consensus among dermatopathologists regarding the melanocytic causes of LM. Therefore, the following histopathological classification represents an attempt to organize the causes into a practicable list.

Dermoscopy (see Chapter 4) will help to better select cases to be submitted to biopsy. It can also be performed during the surgical procedure (see Chapter 4). Persurgical reflectance confocal microscopy also offers the possibility to diagnose, to an almost pathological degree of certitude, the nature of melanocytic proliferations (see Chapter 8).

**Benign melanocytic hyperplasia, focal melanocyte activation ("functional" melanonychia) (Fig. 21.169)**

Benign melanocytic hyperplasia is due to an increase in melanocyte activity and/or number causing a circumscribed pigmented macule in the matrix. When melanocyte hyperplasia indicates the presence of an increased number, there are more than 6.5 cells per mm of basal membrane length of melanin-containing melanocytes within the basal and suprabasal layers of the nail matrix [1122]. Melanocytic hyperplasia in the matrix may also be induced by repeated trauma such as friction and X-irradiation. A circumscribed increased number of normal-looking melanocytes are found in the matrix in the Laugier–Hunziker–Baran syndrome [1077].

**Lentigo simplex and melanocytic nevus**

Lentigo simplex is characterized by a considerable increase in highly active melanocytes accompanied by epidermal hyperplasia. There is a basal proliferation of melanocytes arranged as single cells, rather in nests. Typically, but not always, lentigo is associated with elongation of the rete ridges (lentiginous epithelial hyperplasia). The nature of the underlying melanotic lesion responsible for the pigmented band cannot be determined by clinical examination alone. The same holds true for subungual melanocytic nevi corresponding to a benign melanocytic hyperplasia with at least one nest (Fig. 21.170).

In a series of 22 nevi reported by Tosti et al. [1123], periungual pigmentation was present in one-third of the cases. According to Léauté-Labrèze et al. [1124], since LM can occur at the age when other nevi appear, surgical excision should not be undertaken on different grounds than with other congenital or acquired nevi in children. In a clinical and histopathological study of 40 cases of LM in children below 16 years, Goettmann-Bonvallot et al. [1125] found a lentigo in 12 cases, a nevus in 19 cases, and functional LM in nine children. Ohtsuka et al. [1125] reported a case of congenital nevocytic nevus of the tip of the little finger in a Japanese female infant. This caused discoloration, overcurvature, and subungual hyperkeratosis, giving rise to an appearance similar to the nail of a monkey. An unusual case of extremely large junctional nevus of the nail bed with histological atypia in a 6-year-old Japanese child was described by Pomerance et al. [1125].

Congenital subungual nevi were too often excised as a preventive measure against an exceptional malignant transformation [1125, 1126] and the management of “nevoid nail area melanosis” in Japanese children [603] is still debatable. There is therefore a great deal of controversy about:

- the malignant potential of small congenital nevi
- the malignant potential of subungual nevi
- the relationship of childhood lentigines to the evolution of nevi and to the development of melanomas [1126–1128].

Kawabata et al. [1129] consider that dermoscopic features of melanoma in situ can be distinguished from pigmented nevi. In our experience, on the contrary, most of the dermoscopic features (see Chapter 4, section “Dermoscopy-based differential diagnoses”) observed in congenital (or congenital-type, defined by their occurrence before the age of 5) nevi are very similar to those observed in melanoma. For this reason it is not possible to extrapolate the dermoscopic algorithms used in adults to very early pediatric observations. An international register of congenital and congenital-type nevi of the nail unit has been created by the International Society for Dermoscopy (https://dermoscopy-ids.org/wp-content/uploads/nail_study.pdf) and we encourage systematic reporting of these cases to this register in order to improve our knowledge of this very challenging condition and to better define its management.

**Atypical melanocytic hyperplasia and nail melanoma**

Atypical melanocytic hyperplasia shows an increased number of melanocytes with larger, hyperchromatic, pleomorphic nuclei, more prominent nucleoli, increased mitoses, and long branching dendrites. Thus, atypical melanocytic hyperplasia (Fig. 21.177a) may be considered to be incipient malignant melanoma in situ [1083, 1130].

Melanomas of the nail region are now better understood since the identification and analysis of acro lentiginous melanoma (ALM), the most frequent type [1131, 1132]. Superficial spreading melanoma (SSM) is infrequent and nodular melanoma is very rare in the subungual area, despite Milton et al.’s [1133] findings in Australia (seven cases out of 30 individuals), and Miura
and Jimbow’s [1069] questionnaire survey of 108 cases of subungual melanomas in Japan, indicating that ALM was present in 80% of cases, nodular melanoma in 15%, and SSM in 5%. Some cases are unclassifiable for two main reasons: there may be a histological transition between SSM and ALM [1134], indicating a close biological relationship between the two types; and poor quality of the biopsy specimen [1135].

Approximately 1–3% of melanomas in white people [1065, 1066, 1136] and 15–20% in black people are located in the nail apparatus [1137]. However, since malignant melanoma is rare in black people, the absolute number of ungual melanoma cases in white and black people does not significantly differ. In white people, most patients with SM have a fair complexion, light hair, and blue or hazel eyes. There is no sex predominance. The mean age is 60 years. Most tumors are located on the thumbs and great toes (22 lesions out of 24 subungual melanomas [1138]), but develop more commonly on the foot than on the hand. Melanomas are often asymptomatic, pain and bleeding being rare. The clinical appearance of the tumor varies [1139] but half the patients note a mass below the nail, usually associated with partial destruction of the nail or total loss (Figs 21.176, 21.178).

Periungual infection, ulceration of the nail bed, and granulation tissue occur in about one-third of the patients [1140]. In another third, discoloration of the nail area is the presenting sign.

- Some lesions begin as a longitudinal melanonychia. This pigmented (brown to black) linear streak of variable width runs through the whole length of the visible nail. It was the first feature in six out of 10 patients with malignant melanoma [1065]. After some months or years, the borders of the band widen and become blurred and ulceration appears. It must be stressed that neither the width nor the intensity of the brown pigmentation is proof of, or excludes, subungual melanoma.
- A spot can appear in the matrix or nail bed. This may vary in color from brown to black and may be homogeneous or irregular. It is seldom painful.
• Less frequent is Hutchinson's sign [1141] (Fig. 21.174), an irregular brown-black pigmentation of the matrix, nail bed, nail plate, and surrounding tissues. It represents the radial growth phase of subungual melanoma and has proved to be a valuable clue to the clinical diagnosis of malignancy [1142] after pseudo-Hutchinson's signs have been ruled out. Its presence means that the entire nail apparatus must be removed.

This technique enables serial sections to be examined, which is particularly important in acral lentiginous melanoma in which histology may be difficult to interpret. The radial growth phase of malignant melanoma in the subungual region is easily confused histologically with junctional nevus and the clinician must be wary of a benign histological report in any subungual lesion showing Hutchinson's sign. The vertical phase with its abrupt onset when compared temporally with the slowly evolving radial growth phase is manifested by the focal appearance of a discrete blue, black, or pink nodule in tumors of subungual site causing partial or total permanent destruction of the nail plate [1131].

Approximately 25% of melanomas are amelanotic (Fig. 21.178) and may present as pyogenic granuloma, granulation tissue (Fig. 21.176), ingrowing nail, and mycobacterial infections with nail dystrophy. The risk of misdiagnosis is therefore particularly high in these cases. Unfortunately, dermoscopy criteria of pyogenic granuloma and of amelanotic melanoma are similar. Therefore, nail melanoma must be considered in the differential diagnosis [1143] in all patients affected by unexplained chronic paronychia, whether painful or not, torpid granulomatous ulceration of the proximal nail fold, pyogenic granuloma [1144], pseudoverrucous keratotic alterations of the nail bed and lateral nail groove, and persistence of a lesion following trauma of the nail. Pathological fracture secondary to subungual melanoma may be the presenting sign [1144].

Subungual melanoma may be mimicked by subungual hematoma which is not rare and may even be present without a history of severe trauma (Fig. 21.173). It may follow repeated minor trauma which escapes the patient's attention such as in tennis toe or following trauma from hard ski boots or a windsurf board. Hematoma following isolated trauma usually grows out in one piece rather than as a longitudinal streak due to continuous production of pigment but subungual melanoma following a single injury to the digit was observed in several cases after an interval of between 9 months and 7 years [1060–1062]. Repeated trauma may cause difficulties in differential diagnosis and a non-migrating hematoma should be ruled out.

Alkiewicz and Pfister [1145] suggest that the lesion should be examined with a magnifier, after it has been covered by a drop of oil. Dermoscopy is now used successfully (see Chapter 4). The pigmented nail should be clipped and tested with the argentaffin reaction in order to rule out melanin pigmentation. Subungual hemoglobin is not degraded to hemosiderin and therefore remains Prussian blue negative. Scrapings or small pieces of the nail boiled with water in a test tube give a positive benzidine reaction with conventional Hemastix. However, it has to be stressed that any erosive bleeding tumor will also give a positive benzidine reaction. Therefore, a diagnostic nail biopsy should be performed for the investigation of any persistent, clinically suspicious, pigmented nail lesion [1146]. The difference between blood and melanotic pigment, sometimes rather difficult to discern by routine histological methods, is easily seen by ultrastructural techniques since heme pigment is intracellular while melanin is mainly intracellular [1147].

**Histopathology of subungual melanoma** (Fig. 21.177)

Subungual melanoma is a particular form of acrolentiginous melanoma [569, 1148, 1149]. This type of melanoma is defined by a specific microscopic morphology rather than by its location on palms and soles and under the nails; exceptionally subungual melanoma exhibits criteria for nodular melanoma or for superficial spreading melanoma histopathological subgroups [569, 1063, 1069, 1150]. It is also very important to stress that a major proportion of patients suffering from subungual melanoma have undergone some minor form of surgery or other treatments before the diagnosis of subungual melanoma has been made. This is not only the consequence of patients’ neglect but also of physicians’ misdiagnoses, inadequate biopsy techniques, and insufficient histopathological techniques and knowledge. Thus, the importance of proper biopsy and histopathology for the prognosis cannot be overestimated [1151, 1152].

Recent series as well as our own experience have shown that longitudinal melanonychia in young people is mostly due to lentigines or junctional nevi [611, 610, 653, 1123, 1124, 11534]. Histopathology thus shows melanocytes and nevus cells mainly in the basal zone of the matrix epithelium. Subungual melanoma may arise from suprabasal melanocytes [1154]. Therefore, a biopsy technique was developed that ensures almost scarless healing and gives excellent tissue specimens for histopathological work-up [1155]. This is essentially a superficial, tangential excision of the pigmented lesion of the matrix performed after lifting the nail plate at its proximal third [1155, 1156]. Migration of melanoma cells into suprabasal epidermal layers is a characteristic feature also seen in acral lentiginous melanoma. These cells and cell clusters eventually reach the horny layer or nail plate, respectively. Therefore, clippings of subungual melanoma nail plates sometimes contain pyknotic tumor cells [1157] that retain their protein S100 positivity [1158].
There is usually no difficulty making the histopathological diagnosis of advanced invasive subungual melanoma. Most subungual acrolentiginous melanomas exhibit a lentiginous pattern with pleomorphic, often dendritic atypical melanocytes being arranged singly or in irregular clusters in the basal and suprabasal epithelial layers. Sheets of melanoma cells, spindle, epithelioid, polygonal, small, dendritic, or bizarre and pleomorphic, extend from the epithelium into the dermis. Large round melanoma cells are dispersed throughout the entire epidermis in a pagetoid (SSM-like) pattern. The nodular pattern is rare and shows subepidermal tumor cells usually with scarce junctional cell complexes and at least part of the overlying epithelium is necrotic; in our experience, subungual nodular melanoma appears to be primarily located in the nail bed rather than the matrix. Mixed features of lentiginous and pagetoid patterns are not rare. In particular, the lentiginous type of subungual melanoma may exhibit a dense population of atypical melanocytes in the basal epithelial layers which may give rise to artificial bulla formation due to lack of cohesion between melanoma cells and nail bed and matrix epithelium upon sectioning and is also one cause of nail atrophy in subungual melanoma [1159]. Melanoma cells migrating up to the superficial matrix layers may be included in the nail plate and can be seen microscopically [1158], sometimes even in nail clippings [1157].

Subungual nodular melanoma with no junctional component may be difficult to distinguish from lymphoma or anaplastic and small cell carcinoma as well as other malignant tumors, including metastases, all of which are rare in this location. Several cases of desmoplastic subungual melanoma have been reported [1062, 1139, 1160, 1161] (Fig. 21.179), some with perineural extension. Characteristic intraneural invasion and extension along the median nerve has been demonstrated in a case of acral lentiginous melanoma of the right thumb nail bed [1162]. Subungual melanoma may even extend along the ulnar, median, and musculocutaneous nerves for a distance of 30 cm [1163]. They may also masquerade as fibrous histiocytic tumors [664, 1164] and have even been observed to produce cartilage. Immunohistochemical demonstration of S100 protein or another melanocyte marker such as HMB 45 aids in making the correct diagnosis.

Figure 21.179 (a) Desmoplastic melanoma. (b,c) Histology: case shown in (a). Courtesy of F. Rongioletti.
The most difficult problem in subungual pigmented lesions is to differentiate benign melanocytic hyperplasia that may eventually develop into a benign junctional or compound nevus from the earliest changes of subungual melanoma. Dermoscopy [1059, 1115, 1153, 1165, 1166] provides useful information in this case (for a complete review see Chapter 4). One has always to keep in mind that there are many well-documented cases with histories longer than 20 or 30 years. These cases often started with a light-brown longitudinal stripe in the nail. The authors have observed five cases of subungual melanoma in situ with only a very light longitudinal melanonychia. In the case of a pigmented spot in the matrix or nail bed, the lesion should be completely excised, and serial and step sections are a must. It is common to see only a few melanocytes which tend to be variable in size but some of which have enlarged hyperchromatic nuclei. Serial sections increase the likelihood of detecting limited areas with more pronounced hyperplasia of atypical melanocytes that may be seen in suprabasal layers and exhibit large, hyperchromatic, pleomorphic nuclei. Mitoses are very rare. There may be a sparse mononuclear infiltrate beneath the lesion but it is often inconspicuous. Although macroscopically visible, the melanin is frequently less conspicuous in histological sections, even when Fontana stained. Clear-cut in situ subungual melanoma usually shows junctional nests of melanoma cells. Histopathology of Hutchinson’s melanotic whitlow is virtually identical with the lentiginous pattern of acral lentiginous melanoma in situ of palms and soles [1157]. Atypical melanocytes, often polygonal or even dendritic, are dispersed mainly in the basal layer of the periungual epidermis with relatively few cells being localized suprabasally.

Histopathology is compulsory for the diagnosis of any melanin-induced pigmentation in, under, and around the nail. Both the biopsy techniques [1151, 1152, 1167] and histological techniques, numbers of serial and step sections, as well as the expertise of the investigating dermatopathologist are crucial for the correct diagnosis. However, the clinician is probably the most important person, because he or she has to decide whether to biopsy or not, how to do it, to whom to send the specimen and to carefully or properly mark the tissue so that orientation will be possible in the laboratory. Neither gender, nor localization, nor age must influence the decision for biopsy since subungual melanomas do occur on fingers with esthetic importance as well as in children [1168]. In conclusion, the pathologist must know the details of the clinical picture, and the clinician must be wary of a benign histological report in any subungual lesion showing Hutchinson’s sign [1131].

The development of targeted therapies for advanced melanomas requires precise identification of genomic changes that may occur in the malignant cells. If in cutaneous melanoma mutations of B-Raf represent a potential target for these molecular approaches, in acral lentiginous melanoma, as well as in mucosal or lentigina maligna, mutations of c-kit [1169] have been found more often than in pagetoid (SSM) melanoma subtypes. Determination of the c-kit genotype will therefore certainly be part of the pathological evaluation of nail unit melanoma in future; however recent experience showed that c-Kit mutations were more rarely seen than previously expected in ALM and that available c-Kit blockers (imatinib) were not very efficient in the management of c-Kit mutated metastatic melanomas.

Nail melanoma in childhood
Malignant melanoma is certainly exceptional in childhood and many published cases are debatable. Lyall [1170] reported on a pigmented spot of the tip of the right middle fingernail of a 12-month-old male, not preceded by LM. Pensler et al. [1171] observed a case affecting a white child (but this was not documented). Alvarez-Mendoza et al. [1172] observed a melanoma associated with a black toenail in a Hispanic 9-year-old child (Fig. 21.180). Goettmann-Bonvallot et al. (unpublished data) have seen the appearance of a melanoma in an 18-year-old girl presenting with an LM for several years.

(a)

(b)
Tosti et al. reported two cases of in situ melanoma in 6-month-old and 11-year-old white patients [1128].

By contrast, there are some reports of malignant melanoma in Oriental children. Ohno et al. [1173] presented the case of a 7-year-old girl with an LM who was seen at age 27 with a deformed nail and Hutchinson’s sign. Histology revealed malignant melanoma and lymph node metastases. Mori and Fukui [1174] reported a case of LM starting at age 9, following an injury at age 4, which developed into malignant melanoma at age 32. Uchiyama and Minemura [1175] observed a sudden increase in pigmentation at the base of the right middle fingernail, which appeared 1 month after birth. It then developed into melanoma with lymph node metastasis following a minor injury at the age of 7 years. All except three cases of melanoma in situ of the nail apparatus that have been reported in Japan developed from pigmented bands in the nail after the age of 20 [582]. Kato et al. [1168] described a 2-year-old child with melanoma in situ, Hori et al. [1176] described a 3-year-old girl, and Kiryu [1177] an additional one in the fingernail of another 3-year-old girl. Again, all these cases should be regarded with caution and revision of the original slides by dermatopathology experts should be organized.

Nail melanoma in deeply pigmented subjects
Longitudinal melanonychia is found in 90–100% of individuals with dark phototype (V and VI). The common presenting sign of subungual melanoma is an alteration in color intensity or width of LM. However, the pigmented band shows an indistinct border, sometimes widens rapidly, and the longitudinal streak becomes jet black rather than the normal brown. The diagnosis may be aided by comparing them with the brown streaks in other nails or by occurrence of Hutchinson’s sign.

Nail melanoma in transplant recipients
Of clinical importance is the development of malignant melanomas in transplant recipients. Merkle et al. [1178] reported a slowly enlarging tumor on the tip of the middle finger in a 59-year-old man. This verrucous and erosive non-pigmented tumor involving the distal nail bed was a nodular malignant melanoma in a patient treated with corticosteroids and azathioprine who had undergone kidney transplantation 7 years earlier.

The diagnosis of malignant melanoma may be made only by maintaining a high index of suspicion with any persistent nail bed lesion, irrespective of the presence of pigmentation. Incisional biopsy should be performed in all suspected cases, followed by definitive treatment [1179]. Recent advances in the management of malignant melanoma have been made through knowledge of determinants such as primary depth of invasion, thickness, presence of ulceration, and status of regional lymph nodes [1180].

### Table 21.11 Modalities of treatment of subungual melanoma [1203].

<table>
<thead>
<tr>
<th>Treatment</th>
<th>Reference</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Surgery</strong></td>
<td></td>
</tr>
<tr>
<td>Proximal amputation</td>
<td>Pack and Oropeza 1967 [1204];</td>
</tr>
<tr>
<td></td>
<td>Papachristou and Fortner 1982 [1205]</td>
</tr>
<tr>
<td>Distal amputation</td>
<td>Finley et al. 1994 [1065]; Glat et al. 1996 [1206]; Quinn et al. 1996 [1207]</td>
</tr>
<tr>
<td>Local amputation</td>
<td>Saida and Ohshima 1989 [1070]; Banfield et al. 1998 [1208]</td>
</tr>
<tr>
<td>Nail ablation</td>
<td>Hanek and Binder 1978 [1158]</td>
</tr>
<tr>
<td>Mohs</td>
<td>Banfield et al. 1999 [1066]</td>
</tr>
<tr>
<td>Elective lymph node dissection</td>
<td>Kato et al. 1996 [1209]; Quinn et al. 1996 [1207]</td>
</tr>
<tr>
<td>Sentinel node biopsy</td>
<td>Jigalin and Mainusch 1999 [1210]</td>
</tr>
<tr>
<td><strong>Adjvant therapy</strong></td>
<td></td>
</tr>
<tr>
<td>Chemotherapy</td>
<td>Kato et al. 1996 [1209]</td>
</tr>
<tr>
<td>Dacarbazine</td>
<td></td>
</tr>
<tr>
<td>Nitrosourea</td>
<td></td>
</tr>
<tr>
<td>Vincristine</td>
<td></td>
</tr>
<tr>
<td>Limb perfusion therapy</td>
<td>Lingam et al. 1995 [1211]</td>
</tr>
<tr>
<td>Radiotherapy</td>
<td>Krige et al. 1995 [1071]</td>
</tr>
<tr>
<td>Other modalities</td>
<td>No reported experience in subungual melanoma</td>
</tr>
<tr>
<td>Interferon</td>
<td></td>
</tr>
<tr>
<td>Interleukin</td>
<td></td>
</tr>
<tr>
<td>Vaccination therapy</td>
<td></td>
</tr>
</tbody>
</table>

### Treatment of the nail unit melanoma
Several modalities of treatment of subungual melanoma have been suggested (Table 21.11). In fact, treatment for nail unit melanomas (NUMs) is surgical. Increasingly, authors report treatment of in situ and microinvasive NUMs (Breslow <0.5 mm) by “en bloc” removal of the nail unit, which seems reasonable according to the published data, even if there is not a high level of evidence [1181, 1182]. There are three main issues in the management of NUMs in situ:

1) The certainty that the melanoma really is in situ. The biopsy of suspected longitudinal melanonychia should always be excisional and not incisional. The whole specimen may then be examined by the pathologist on serial cuts, to ensure that the melanoma remains in situ throughout the tumor.

2) The width of the lateral margins. It has been demonstrated, using genomic hybridization and fluorescent in situ hybridization, that melanocytic cells with genetic amplifications were detected in histopathologically normal skin, with a mean extension of 6.1 mm (in situ melanomas) and 4.5 mm (invasive melanomas)
beyond the histopathological margin. Genetic profiling of these cells indicated that they represent an early phase of disease preceding melanoma in situ. The melanoma cells extend significantly into seemingly normal skin. These cells provide a plausible explanation for the tendency of certain melanoma types to recur locally, despite apparently having undergone complete excision [1183]. This may explain why, in studies acknowledging wide local excision of 5–10 mm, the recurrence rate is almost nil for in situ melanomas.

3) The thickness of the deep margin. A recent study on cadavers evaluated the distance from the lowest base of the nail matrix to the phalangeal bony surface. The average distance in all digits was 0.90 mm, and the shortest distance among the measured specimens was 0.27 mm [1184]. Thus, some soft tissue may remain adherent to the bone after en bloc ablation of the nail unit because of the paucity of the subungual soft tissue between the tumor and the bone beneath the nail apparatus. Only very skilled surgeons are able to perform so-called “skeletization.” Consequently, Chow et al. proposed removing a 1 mm horizontal slice of the underlying bone using an oscillating saw [1185]. This ensures better control of the deep margin and ensures preservation of the length of the digit. To be efficient, this procedure should involve the proximal bony phalanx underlying the matrix, without harming the extensor tendon, taking into account that in the great toes the extensor tendon lies between the matrix and the phalanx and extends dorsally to the distal aspect of the distal phalanx [1186].

Thus, surgical treatment of melanoma in situ should include en bloc incision of the nail unit, with at least 6 mm margins around the anatomical boundaries of the nail unit (including the lateral horns of the matrix), skimming the periosteum, leading to a real “skeletization.” If the surgeon can achieve it, removal of a slice of the most superficial part of the bone should be performed. In the presence of an existing Hutchinson’s sign, the excision lines should extend 6 mm beyond the borders of the pigmentation characterizing the horizontal spread of disease. Closure may be achieved by either secondary intention or full-thickness grafting [1187–1191]. The authors prefer secondary intention for toes, as the graft may suffer because of footwear and accidental shock. For fingers, grafting gives a more esthetic aspect: there is no retraction, the shape of the graft is similar to that of a nail, and the graft offers padding to the underlying bone, as opposed to secondary intention healing, where the superficial tissues adhere to the bone. Some authors have utilized artificial dermis for closure [1192].

The recent development of intraoperative reflectance confocal microscopy examination of the nail matrix has enabled one-step surgical management of in situ or minimally invasive melanomas, reducing dramatically the duration of postoperative disability [1193].

For invasive NUMs, as there is no evidence that aggressive amputation is associated with higher survival rates, amputation should be aimed at retaining the greatest function possible [1194].

Sentinel lymph node biopsy (SLNB) helps to stage the cancer and dictates further adjunctive therapy. In melanoma SLNB is nowadays considered as a staging method; it does not improve survival but helps to better schedule subsequent follow-up and, when available, adjuvant therapy [1195–1200].

Future developments

Finally, knowledge of the gene expression profile may have important implications in disease management and treatment, thanks to the development of new drugs, such as KIT-and MAPK-targeted kinase inhibitors [1201]. It has recently been shown that TERT gene amplification is associated with poor outcome in acral lentiginous melanoma [1202].

Blue nevus

Soyer and Kerl [1212] found a slightly infiltrated black area, well demarcated, with a small periungual nodule (Fig. 21.181a) on the dorsum of the left great toe of a 4-year-old girl. Several pinhead-sized satellite nodules were found in the neighboring skin with enlarged lymph nodes of the left groin. Epithelioid, dendritic, and spindle-shaped melanocytes were found in the capsule and in some parts of certain lymph nodes. The case was interpreted as an example of periungual combined nevus with benign lymph node metastasis (metastasizing pseudomelanoma) from the blue nevus component.

Vidal et al. [1213] reported on distal subungual blue nevus (Fig. 21.181b,c) as an asymptomatic nodule, present since birth, and growing slowly on the right great toe. Histology of the 9 mm diameter nodule demonstrated elongated, slightly spindly cells with long branching dendritic processes. Two additional cases have been published by us; neither clinical nor dermoscopic features are sufficient to make a certain diagnosis without pathological examination of a biopsy [1214, 1215]. These cells were arranged in fascicles and were dispersed as solitary units among collagen bundles. Dermal melanocytes were mostly orientated with their long axes parallel to the epidermis and many were filled with fine granules of melanin.

Atypical blue nevus is an exceptional tumor [1216] which may involve the nail matrix (E. Duhard, unpublished data) (Fig. 21.181d,f).
Abnormal nevoblast migration may mimic neurofibromatosis [1217], where hundreds of papules and nodules on both feet and toes have been reported as intradermal nevi. A similar clinical presentation was shown in a black male [1218]. The main difference was the presence of only blue nevi in the latter case. Leu 7 and myelin basic protein were negative which also ruled out neurofibromatosis [1219]. However, is the case of nail melanoma of the great toe of a neurofibromatosis patient reported by Karakayali et al. [1220] just a coincidence or an association? Another case of multiple congenital melanocytic
nevi with prominent neurofibroma-like lesions has also been reported [1221].

**Evolution and prognosis of subungual melanoma**

(Fig. 21.183)

Ungual melanomas are generally assumed to have a poor prognosis [569, 1158]. This is due to the delay in diagnosis which, in turn, is the cause of the presentation of very thick melanomas in many patients. However, for comparable levels of invasion (Breslow’s micrographic index), the prognosis of ungual melanoma does not significantly differ from the prognosis of other types of cutaneous melanomas. The appearance of pigmented streaks in the nail plates is an unusual metastatic manifestation of malignant melanoma. In a cohort of 40 patients with subungual melanoma, 31 were in clinical stage I and nine in stage II; 35 patients were treated with amputation and 33 of them also underwent regional lymph node dissection. Only one patient in clinical stage I already had lymph node metastases whereas all stage II patients had positive lymph nodes. Elective lymph node dissection was therefore not supported for clinical stage I [1222].
We have therefore adopted sentinel lymph node (SLN) dissection for invasive subungual melanoma [1155]. Elective lymph node dissection has never been proven efficient [1206, 1223, 1224]. "Sentinel node" biopsy, despite the absence of proven impact on survival, is widely used in melanomas with Breslow's index higher than 0.7 mm, or with ulceration, or with mitotic index greater than 1/mm². It is also widely accepted that complementary lymph node dissection should be performed where there is histopathology-proven invasion of the sentinel node. The main advantage of this technique is a more accurate prognostic subclassification of the patients (the survival rate in cases of positive SLN drops from 91% at 5 years to about 41%). This prognostic information could become of interest if any adjuvant therapy proves its efficacy in stage II patients in future. Adjuvant therapies including isolated regional perfusion with cytotoxic drugs [1225] did not improve the survival rate.

**Spontaneous regression of melanocytic lesions**

Longitudinal melanonychia, as a sign of the “nevoid nail area melanosis” observed in Japanese children, may demonstrate spontaneous regression and even disappearance [1087] (Fig. 21.184). The histological features of these pigmented lesions are lacking. LM from a matrix nevus was also observed to fade with time [1123] (Fig. 21.185). Complete disappearance of LM occurring in a 4-year-old child (Fig. 21.186).

---

**Figure 21.184** (a) Congenital melanonychia with pseudo-Hutchinson's sign. (b) Same patient several years later. Courtesy of I. Kikuchi.

**Figure 21.185** (a) Longitudinal melanonychia in a 9-month-old baby. (b) Finger shown in (a) 4 months afterwards. Note the fading of the band. (c) Lateral–longitudinal excisional biopsy. (d) Histology showing a typical nevus: case shown in (a). Courtesy of A. Tosti.
white child has been observed after 16 years in a patient of Grosshans [1226] (Fig. 21.186).

Pathologists now more readily recognize the subtle features of histological regression since step sections through the entire block are more often performed. Regression was found in 27.1% of SSM and 17.4% of lentigo maligna melanomas and was not identified in nodular melanomas [1227]. Histological regression, however, played only a marginal role as a prognostic factor in SSM, deriving its significance mainly from its close relationship to the thickness of the melanoma.

Clinical examples of spontaneous regression of malignant melanomas of the nail apparatus are exceptional (Fig. 21.187) and have not been histologically documented.

References


Tumors of the Nail Apparatus and Adjacent Tissues


Chapter 21


Tumors of the Nail Apparatus and Adjacent Tissues


Tumors of the Nail Apparatus and Adjacent Tissues


Chapter 21


Chapter 21


Tumors of the Nail Apparatus and Adjacent Tissues


Chapter 21


1006 Winer LH. (1952). Solitary congenital nodular calcification of the skin. AMA Arch Derm Syphilol. 66 (2): 204–211.


Chapter 21


Chapter 21


Chapter 22

Nail Surgery

Bertrand Richert1, Eckart Haneke2, Elvin G. Zook3, and Robert Baran4

1 Department of Dermatology, Brugmann, St Pierre and Queen Fabiola University Hospitals, Université Libre de Bruxelles, Brussels, Belgium
2 Department of Dermatology, University of Bern, Bern, Switzerland; Centro de Dermatologia Epidemis, Porto, Portugal; Department of Dermatology, University of Ghent, Ghent, Belgium
3 Formerly, Plastic Surgery Institute, Southern Illinois University, School of Medicine, Springfield, IL, USA
4 Hon. Pr. of the University of Franche-Comté; Nail Disease Center, Cannes, France

Introduction

This chapter has drawn on the skills of four experts in nail surgery working in different countries in the specialties of dermatological surgery and hand surgery. The surgery of the nail and its associated structures has generated considerable interest during the last decade; a deformed nail has always been a cosmetic handicap but, until recently, the possibilities for surgical correction were limited. The application by the dermatologist of the techniques of plastic surgery and the more refined skills of the specialized hand surgeon have brought fresh optimism to the field. The objectives of nail surgery are:

- to facilitate diagnosis with adequate nail unit biopsy
- to ensure complete removal of local tumors with best cosmetic result
- to alleviate pain from trauma, tumor, or dystrophy
- to treat infection, which may or may not be directly associated
- to correct or prevent anatomical, traumatic, congenital, infectious, parasitic, or iatrogenic deformities.
These objectives are interrelated and must be viewed as a therapeutic whole.

This chapter covers most common surgical procedures on the nail unit. Specific procedures for resection of a tumor are detailed in the corresponding paragraphs in Chapter 21.

**Surgical anatomy**

Detailed nail unit anatomy is presented in Chapter 1. Here only the main aspects relating to nail surgery will be outlined (Fig. 22.1).

- **The nail plate** adheres firmly to its bed but is very loosely attached to the matrix. Its thickness increases from proximal to distal and is proportional to the size of the matrix. Its shape follows that of the matrix. If the latter is injured, the plate will be dystrophic.

- **The proximal nail fold** (PNF) is a skin fold overlying most of the matrix. Its dorsal and ventral surface merge to form the cuticle. Its ventral part is called the eponychium. The latter has a unique sealing function. Disruption of this seal is responsible for inflammatory or infectious conditions. The fusion of its undersurface with the matrix will form a specific scar called dorsal pterygium. Loss of the eponychium will eliminate the shine on the nail and cause roughness of the surface.

- **The matrix** is solely responsible for the production of the nail plate [1]. The proximal portion of the matrix produces the upper third of the nail plate and its distal part the lower two-thirds [2] (Fig. 22.2). Thus, surgery on the distal matrix is at very low risk of inducing nail dystrophy, because the upper layers of the nail plate cover the defect. The matrix rests on the base of the bony phalanx and forms a crescent with posterior–inferior concavity. There is very little subdermal fat under the matrix. The most proximal part of the matrix lies over the very distal fibers of the extensor tendon. There is little chance of this tendon being injured, unless radical surgery such as removal of the whole nail unit is undertaken. On the great toenails, both lateral ends of the crescent (lateral horns of the matrix) may reach up to or even beyond the midline of the lateral aspect of the great toe. This is the reason why spicules arise if the lateral matrix horns are not completely removed. In the distal matrix, there are two compartments of melanocytes: one that is dormant and one that is functionally differentiated. This is why about 85% of longitudinal melanonychias originate in the distal matrix [3].

- **The nail bed** (also called the sterile matrix by some hand surgeons as it does not produce nail keratin) adheres very firmly to the bone and the plate. On the nail bed run longitudinal ridges that are responsible for its tight adherence to the undersurface of the plate. These ridges should not be injured during nail avulsion, as this would impair the bed–plate adherence. However, the nail bed regenerates very easily and because nail dystrophies are very unlikely, the nail surgeon should not be afraid of working on it.

---

**Figure 22.1** The anatomy of the nail. (a) Sagittal section through the distal phalanx. (b) Dorsal view and estimates of nail growth rate. C, cuticle; DP, distal phalangeal bone; E, eponychium; ET, extensor tendon; FT, flexor tendon; HO, hyponychium; L, lunula; M, matrix; NP, nail plate; PNF, proximal nail fold.

**Figure 22.2** Nail-producing epithelia of the nail. The blue area is the apical matrix producing the dorsal nail layer of the nail, the red is the mid-matrix producing the bulk of the nail thickness, the pink is the distal matrix responsible for the deep nail layer, and the brown is the nail bed producing the ungual (nail bed) keratin. C, cuticle; E, eponychium; HO, hyponychium; L, lunula; M, matrix; NB, nail bed; NP, nail plate; PNF, proximal nail fold.
● The **hyponychium** is the junction between the distal nail bed and the skin of the fingertip. It seals the virtual space between the skin and the subungual region.

● The **perionychium** consists of the paronychium (surrounding soft tissue) and the matrix and nail bed [4].

● **Vascularization** of the nail unit rests on three arcades arising from the digital proper artery.

● **Innervation** of the nail unit comes from one branch of the dorsal digital nerve and one ventral branch from the palmar digital nerve.

**Preoperative measures and preparation of the patient**

**Patient history, information on the surgical procedure, and return to work**

A thorough and efficient preoperative evaluation is mandatory for all patients undergoing nail surgery as for any other dermatological operation. Screening for underlying diseases, especially focusing on any cause of vascular impairment of the extremities (diabetes, Raynaud disease, smoking, arteriopathy), current medication and potential allergies (latex, povidone-iodine, antibiotics, pain killers of any type, anesthetics), should be performed. Management of common perioperative issues in a proactive and standardized manner, with opportunity to individualize decisions when clinical conditions indicate, is an efficient and optimal approach [5]. The preoperative consultation should assess all aspects of the planned surgical procedure. Drawings are most eloquent. Surgical complications (see later in the chapter) as well as transitory and permanent nail dystrophy should clearly be reviewed with the patient. Pain is a main concern for patients: they are mostly frightened by the anesthesia. Explanation about the procedure is of great help. If dealing with “needle phobic” patients, do not hesitate to propose anesthetic creams prior to surgery (see “Local regional anesthesia”). Patients should also be reassured about the management of postoperative pain and removal of the dressing. Information about possible long-standing postoperative dysesthesia should be given. Patients should be offered a flyer containing all preoperative information. It is of utmost importance to try to evaluate as accurately as possible the healing time and the impact of the surgery on the patient’s professional activity. Remember to inform the patient that the limb has to be elevated for 48h (this means no driving at all), so that people living alone or elderly patients can make arrangements for accommodation of their activities of daily life.

**Medical imaging**

Medical imaging is detailed in Part II. Dermoscopy should be performed as often as possible as it provides the surgeon with a great deal of information because it magnifies beautifully all external nail structures (Fig. 22.3a,b). It is of great help in determining the limits of a tumor. Most commonly, inadequate medical imaging is performed. One should remember that standard radiography remains the gold standard imaging. This easy, non-invasive, and cheap examination may reveal alterations of the bony phalanx that may contribute to the diagnosis and guide the surgical treatment of many conditions. It is not sufficiently often performed before nail surgery.

Magnetic resonance imaging (MRI), when available with an adequate digital coil, may give a precise location of a tumor that is not clinically visible (e.g. glomus tumor) [6]. Its main indications are vascular and cystic lesions (e.g. glomus tumor and myxoid pseudocyst). For some special indications, thin section computed tomography

![Figure 22.3 (a) Painful fissure at the junction of the proximal and lateral nail folds. Several topical treatments were attempted by several physicians without improvement. (b) Dermoscopy reveals that this is a viral wart of the eponychium.](image-url)
is of great help (osteoid osteoma). Ultrasound is not yet routine in preoperative diagnostics. It is very helpful to have preoperative photographs of the diseased nail [7].

Premedication

Premedication may be useful in anxious patients. Short-acting molecules should be preferred: hydroxyzine or diazepines orally or sublingually, the latter being quicker. The combination of hydroxyzine 25 mg the night before operation with lorazepam sublingually 1 h prior to surgery is very efficient [8]. Midazolam is favored by some surgeons as it offers short-acting hypnotic and anxiolytic and retrograde amnestic properties [7].

Antibiotic prophylaxis

Antibiotic prophylaxis in dermatological surgery is poorly understood, and data on its use are lacking. Prophylaxis is indicated for the prevention of endocarditis and postoperative infection, as well as surgical site infection. Antibiotic prophylaxis should reflect the recommendations of recent prospective studies. Prophylactic antibiotics are only indicated for patients with high-risk cardiac conditions and patients with prosthetic joints at high risk for joint infection. Prophylactic antibiotics are recommended when the surgical site is infected and for procedures on the lower extremities [9].

Although no evidence supports this practice, some practitioners recommend antibiotic prophylaxis for nail procedures that carry a higher risk of postoperative infection, such as in poorly monitored diabetic patients and bone surgery. All surgical procedures should be performed under full sterile conditions [9, 10]. For more invasive surgery (exostosis, surgery of malalignment), whenever possible, surgical facilities should meet orthopedic surgical standards [7].

Preoperative cleaning of the surgical site

The lack of cleanliness of patients’ digits or toes on the day of surgery is sometimes amazing! It is recommended that patients who have jobs in which dirt gets under their nails soak their hand/foot in soapy water and clean them with a scrubbing brush for several days before surgery. Ask ladies to remove their nail lacquer [11]. There is no study on the use of antiseptic soaps in the days prior to surgery, has been recommended as it significantly reduced the intraoperative and postoperative bacterial counts [15]. Another study mentions that incorporation of alcohol and povidone-iodine into the preoperative nail preparation may help to reduce the bacterial load [17]. The most disturbing finding in these studies is that the nail remains contaminated after any of the preoperative nail preparation methods studied. This suggests that all efforts to reduce the bacterial load should be used [15]. However, it is amazing to notice how nail surgery is associated with very few postoperative infections.

Disinfection of the surgical field

A footbath with chlorhexidine gluconate, 20 min before surgery, has been recommended as it significantly reduced the intraoperative and postoperative bacterial counts [15]. Brushing the nail does not decrease bacterial numbers [16]. A footbath with chlorhexidine gluconate, 20 min before surgery, has been recommended as it significantly reduced the intraoperative and postoperative bacterial counts [15]. Brushing the nail does not decrease bacterial numbers [16]. Another study mentions that incorporation of alcohol and povidone-iodine into the preoperative nail preparation may help to reduce the bacterial load [17]. The most disturbing finding in these studies is that the nail remains contaminated after any of the preoperative nail preparation methods studied. This suggests that all efforts to reduce the bacterial load should be used [15]. However, it is amazing to notice how nail surgery is associated with very few postoperative infections.

Instrumentation

Although nail surgery is carried out on a surface of area less than 4 cm², it will encounter both very thick and hard structures (nail plate and bone) and thin and fragile tissues (nail bed and matrix). For nail plate surgery, instruments must be sturdy and resistant. For nail bed and nail matrix surgery, instruments should be as delicate as possible, as one may use for fine flaps on the face.

A few specific instruments are needed for nail surgery. An elevator is mandatory to avulse the nail atraumatically by gently detaching the nail plate from the bed and PNF. Several elevators are available (Fig. 22.4a,b): the Freer septum elevator is probably the most widely used with its round and smooth tip at each extremity and its
Nail Surgery

curved shape that is perfectly adapted to the longitudinal shape of the nail; the Lempert elevator is a narrower variant with a less curved extremity; and the Locke elevator is a narrower and flat variant (Fig. 22.4c) [18]. Instruments from other specialties may be used: the dental spatula is shorter, easy to handle, and has an extremity of intermediate size (3 mm), with sharp corners and an adapted angle.

Nippers are of utmost importance for cutting the nail plate. For cutting thin nails (as in children) straight scissors will do. For cutting thick nails, the dual action nail nipper (Fig. 22.5a) is invaluable: it has nicely adapted beveled jaws and its four hinges will allow cutting of the thickest pachyonychia. The English nail splitter (Fig. 22.5b) is unique with its anvil-like lower jaw. Its
upper surface slides under the nail plate while the upper jaw has an inferior cutting edge allowing the cutting of thick nails. The main drawback of this instrument is that the thickness of the lower jaw always induces a lateral onycholysis ahead of the cutting line. *Straight nail nippers* (Fig. 22.5c) are probably the most adequate for cutting a nail of normal thickness: they have sharp cutting jaws, thin beveled extremities, and a flat undersurface. They allow cutting of the nail with almost no extra lateral onycholysis.

**Magnification loupes** are of incomparable help to perform the most precise surgery. *Teflon™ coated surgical blades* slide smoothly through the tissue being cut [19]. These blades are especially indicated for matrix tangential excision.

The *Beaver blades* (or miniblade system) provide a range of variously shaped cutting edges. They give the surgeon added precision.

**Skin hooks** avoid pulling on fragile tissue edges with forceps, allowing an atraumatic pull, even for a long time. The most common are *Gillies* skin hooks.

A *bone rongeur* should be available for removal of bone tumors.

A *tourniquet* is always required, as the surgical field needs to remain bloodless in all instances, especially when performing matrix cauterization. The Penrose drain is widely used. It is wrapped around the base of the digit and its two ends are clamped together with a sturdy hemostat. This is especially adapted for toenail surgery. It has been shown that this technique delivers high and unreliable pressure [20] and it is not recommended for digits. Tunable zip-ties that have been proposed as digital tourniquets should not be used for the same reason [21]. An alternative is to use a tourniquet made from a piece of a latex glove finger cut at both extremities. Rolled onto the finger or toe, it provides exsanguination (Fig. 22.6a). It is easily available and suitable for both toe and fingernail surgery but the main risk is forgetting to remove it after the surgery. For fingernail surgery, it is best to use a sterile glove, placed on a disinfected hand, under full aseptic conditions. The top of the glove fingertips is cut off and rolled back to the base of the proximal phalanx (Fig. 22.6b). This technique exsanguinates the digit and the whole glove will not be forgotten at the end of the procedure. The *T-Ring* is a commercially available single-use tourniquet which has the great advantage of first exsanguinating the finger and providing a safe and controlled pressure of 160 mmHg (Fig. 22.6c).

A *basic nail surgery tray* should include the following:

- tourniquet
- elevator
- nail nippers
- *Bard-Parker* blade holder, with blades no. 15 or 15C
- fine Adson toothed 2 × 1 forceps
- fine straight scissors, *Iris* or *Graddle* type, for cutting tissues
- fine curved scissors, *Iris* or *Graddle* type, for undermining
- needle holder, with smooth jaws, for holding thin needles (5/0 or less) for suturing the bed and/or the matrix
- needle holder, with serrated jaws, for holding larger needles (4/0 and over) for suturing the skin and through the nail
- suture cutting scissors (the cheapest heavy straight scissors will do).
- sturdy straight hemostat, at least two (they are very useful to grasp thick nails for avulsion)
- curette, excavator type (*Besnier* lupus or *Volkmann* curettes), fenestrated or not
- non-absorbable 3/0 and 4/0 sutures
- absorbable 4/0 and 5/0 sutures.

### Anesthesia

#### Local regional anesthesia

A good knowledge of the nerve anatomy of the digits (see Chapter 1), as well as of the techniques of anesthesia of the nail unit, is a prerequisite to ensure comfortable nail surgery both for the patient and surgeon. Paired palmar and plantar nerves lie at the sides of the flexor tendon sheath and digital proper arteries. These digital nerves divide into three main branches just distal to the distal interphalangeal joint. One branch goes to the nail bed, one to the tip of the digit, and the other onto the pulp (Fig. 22.7) [22]. The aim of the procedure is to block the dorsal and the ventral branches to obtain complete numbing of the digit/toe.

Checking for any history of allergy to lidocaine or bupivacaine or parabens (contained in both as preservative) is part of the preoperative consultation. Local anesthetics may be contraindicated in patients with cardiac disease such as heart block [23].

For most people, nail surgery is an emotional experience. As when visiting the dentist, patients are more often more apprehensive about the needle stick than the actual procedure. Premedication may be useful in anxious patients (see “Premedication”). In children and needle phobic patients several tricks may reduce the pain from the needle prick. The use of *EMLA cream* under an occlusive dressing, at least 1 h prior to the local anesthesia, will alleviate the pain from needle insertion [24] but not the one from the swelling and deposition of the local anesthetic [25].

Gentle freezing (ice packs, topical cryogen spray) may reduce the discomfort from the needle stick [10]. Pressure and vibration at the site of injection for several
minutes minimize the concurrent pain from the needle stick [26].

Anesthetic products
Plain lidocaine 1% or 2% is the reference local anesthetic. Plain 2% should be preferred as it seems slightly more efficient [18].

Lidocaine with epinephrine has been shown to be safe for digital anesthesia, but there remains very deeply ingrained resistance to its use for digital anesthesia. It is widely thought that it will lead to irreversible digital artery vasospasm [27]. Multiple studies involving thousands of patients support the premise that the use of lidocaine with epinephrine is safe in the digits [28–32]. The use of lidocaine with epinephrine has clear advantages such as quicker onset, fewer reinforcement doses, less need for special maneuvers to stop bleeding, and longer total time of postoperative analgesia [31]. However, a recent publication from the Cochrane Group showed that there are only limited data available and that

Figure 22.6 (a) Tourniquet made from latex glove finger. (b) A sterile glove may be used as tourniquet and sterile field at the same time. (c) Commercially available tourniquet (T‐Ring). Courtesy of N. Jellinek.
evidence is insufficient to recommend use or avoidance of epinephrine in digital nerve blocks according to the published data. The evidence provided in this review indicates that addition of epinephrine to lidocaine may prolong the duration of anesthesia and reduce the risk of bleeding during surgery, although the quality of the evidence is low. They conclude that large prospective trials are required [33]. This strengthens the opinion of the authors, who believe that lidocaine with epinephrine is of little help when performing nail surgery [32], in contrast to some others [34]. Most surgical nail procedures require a completely bloodless field that is only achieved when using a tourniquet and not with an epinephrine-containing anesthetic.

Bupivacaine 0.5% acts for 8 h [35]. Injecting 0.5–1 mL of bupivacaine immediately postoperatively as a distal digital block will first act as a volumetric tourniquet – the liquid load pressing on the digital proper arteries will stop any postoperative bleeding – and, second, will ensure a very comfortable postoperative period for the patient.

Ropivacaine has the same quick onset as lidocaine but provides better postoperative pain relief (up to 9 h) [36, 37] and is less cardiotoxic than bupivacaine [38]. Mean time to regain full sensation is over 8 h for 2 mg/mL. Ropivacaine appears to produce vasoconstriction at low dosages [39]. For all these reasons, the authors routinely use ropivacaine 2 mg/mL with a very comfortable anesthesia and postoperative period for patients. The use of this anesthetic is restricted to patients without any history of vasospastic disease, diabetes mellitus, Raynaud disease, heavy tobacco use, etc. If a painful postoperative period is expected, an injection of ropivacaine 10 mg/mL postoperatively may provide up to 18 h of complete anesthesia.

Materials
Luer-Lock syringes or dental syringes (Fig. 22.8) are mandatory for any type of anesthesia at the nail apparatus, as these are high-resistance injections (weak dilatation of tissues). Very thin needles (30G) will decrease the pain from puncture. Their size will also limit the anesthetic flow, inducing very slowly progressive swelling of the soft tissues. It is common for the physician to spend more time injecting the anesthetic than performing the surgical procedure. The pain from injection is clearly linked to the speed of injection [40].
Needleless injection systems for digital blocks have been proposed for “needle phobic” and young patients. This is no different from a disposable DermoJet. The liquid is delivered in an aerosol form subcutaneously to a depth of 5–8 mm, fanning out on maximum penetration to a width of 8–10 mm. This technique is not reliable because it requires in all patients an additional anesthetic administration of 3 mL to achieve adequate anesthesia of the tip of the finger/toe [41].

Procedures
It is best to have patients in a reclining position during the administration of anesthesia in the event that a vasovagal episode occurs. It is judicious to inform the patient when the needle stick is about to occur in order to avoid a dangerous reflex jerk [42].

Proximal digital block (formerly called ring block)
The term “ring block” should be abandoned as it suggests injection of anesthetic all around the base of the finger. This historical technique induces constriction of the blood flow through a tourniquet of fluid at the base of the proximal phalanx; it should no longer be performed. The proximal digital block is the updated and adequate procedure of this type of anesthesia. With the patient’s hand pronated, the needle punctures the skin in the midline of the lateral aspect of the proximal phalanx, at an angle of 45° from the proximal bony phalanx, 1 cm distal to the interdigital web. The needle is pushed until there is bone contact, whereupon 1.5–2 mL of anesthetic is deposited to numb the digital nerve. The procedure is then repeated on the opposite side of the digit to complete the block. A complete block is usually achieved in 10–15 min, sometimes more.

Distal digital block (wing block)
This is the most useful in routine nail surgery as it acts immediately. The skin is penetrated at a point about 1 cm proximal and lateral to the junction of the PNF and the lateral nail fold. By directing the needle at a 45° angle distally down to the bone (Fig. 22.9a), about 0.5 mL of anesthetic is slowly deposited. Resistance to injection suggests that the needle tip has penetrated some fibrous tissue such as ligament or the periosteum. Careful withdrawal of the needle will result in a free flow. Blanching of the lateral part of the lunula is often noticed. This injection will anesthetize the dorsal nerve. The needle is then slightly withdrawn and set back upright and pushed downwards, skimming the lateral aspect of the bony phalanx, until it reaches the ventral pulp. Another 0.5 mL of anesthetic is injected there (Fig. 22.9b).

Distal wing block
This is indeed a true periungual block. The first step of the procedure is identical to that of the distal digital block: the needle is inserted about 1 cm proximal and lateral to the junction of the PNF and the lateral nail fold, at a 45° angle, down to the bone, and about 0.5 mL of anesthetic is slowly injected. The needle is then withdrawn and pushed distally into the lateral nail fold, where some more anesthetic is deposited. Injections are repeated several times at the previously anesthetized site while progressing up to the tip of the digit (Fig. 22.10a). The infusion and bleaching of the lateral nail fold resembles a wing as it progresses distally [43]. This will provide anesthesia of half of the nail apparatus. For complete anesthesia, the procedure should be repeated on the opposite side. The procedure requires about 1.5 mL per side. When finished, the entire digital tip appears swollen and white (Fig. 22.10b).
Matrical block

This technique allows immediate anesthesia of the PNF, the matrical area, and the proximal half of the nail bed. It is performed in the same manner as intramatrical injection of corticosteroids. The needle punctures the skin in the midline of the PNF, about 5–7 mm proximal to the cuticle, bezel upwards, at 60° from the surface of the PNF. It is pushed forward until it touches the bone, then slightly withdrawn (1 mm backwards). The anesthetic is very slowly injected, with progressive blanching of the lunula and the proximal nail bed (Fig. 22.11). If reflection of the PNF is expected, infiltration of the junction of the lateral nail fold and PNF is mandatory.

Transthecal block

This technique involves a single palmar percutaneous injection of lidocaine into the space of the flexor tendon sheath, with centrifugal diffusion and complete anesthesia of the digital nerves of the finger [44]. The procedure requires a small volume (3 mL) of plain lidocaine, has a rapid onset of anesthesia (3–4 min), and involves little risk of direct mechanical trauma to the neurovascular bundles as the needle is not placed in the vicinity of vascular structures. This technique is only indicated for anesthesia of the index, middle, and ring fingers. Due to anatomical variations, it is not reliable for the first and fifth digits.

With the hand supinated to expose its palmar aspect, the needle is inserted at the palmar digital crease, sharply

Figure 22.10 (a) Wing block. (b) Blanching of the distal tip after wing block.

Figure 22.11 Matrical block.
through both flexor tendon and tendon sheath, straight to the bone, perpendicular to the volar skin (Fig. 22.12).
The needle is then slightly withdrawn from the bone while gentle pressure is applied on the plunger of the syringe. Immediately, as the needle tip lumen clears the tendon on slow pull-back of the needle, the anesthetic solution flows easily at low pressure into the tendon sheath. Immediately after infusion, the patient should keep the limb hanging downwards to assist diffusion of the anesthetic distally. Full block is obtained in about 5 min [45].

**Hyponychial block**
This block is painful and is not recommended.

**Metacarpal block**
Metacarpal blocks and webspaces blocks are useful for anesthetizing the lateral aspect of adjacent digits. Digital nerve block performed in the web or in the metacarpal area is safe because hydrostatic pressure of the injection creates a tourniquet effect. A wheal is raised with 2 mL of the local anesthetic agent at the level of the digital nerve, on the dorsum of the hand 2–3 cm proximal to the web, which is volar to the deep transverse intermetacarpal ligament. The needle is reinserted on the opposite side of the metacarpal to block the other digital nerve (Fig. 22.13). It takes 10–15 min for the anesthesia to develop.

**Wrist block** [46, 47]
This is the technique of choice when treating several fingertips or when there is infection or vascular impairment in the affected digits. This procedure involves truncal infiltration of the median and ulnar nerves (Fig. 22.14).

**Median nerve block**
Locate the palmaris longus tendon and flexor carpi radialis by asking the patient to flex the hand against resistance. At the distal crease at the wrist between the two tendons, raise a small skin wheal with a 2 cm needle and advance the needle about 8–12 mm. Care should be exercised so that the nerve is not transfixied. Advance the needle slowly to contact the nerve if paresthesia is desired. When it is elicited, withdraw the needle 1–2 mm and inject 5–8 mL of suitable anesthetic.

**Ulnar nerve block**
At the proximal crease of the wrist, immediately medial to the ulna, advance a 2 cm needle diagonally pointing posteriorly and cephalad until the medial surface of the ulna is contacted. Withdraw the needle a few millimeters and then re-advance in a slightly more medial direction until the tip of the needle is felt tenting the skin of the dorsal surface of the arm by the operator’s other hand. Aspirate, to ensure absence of blood, and then inject 8–10 mL of suitable local anesthetic.
while withdrawing the needle. The injection site has to traverse the course of the ulnar nerve and its branches. The success rate is almost 100% with this block.

Radial nerve block To inject the radial nerve, the sharp edge of the curve of the lower end of the radius is used as a guide. The anesthetic is placed subcutaneously in the deep layer of fat, starting at the edge of the radius 5–8 cm above the wrist, where the nerve emerges under the brachioradialis tendon.

General anesthesia

General anesthesia is very uncommonly used in nail surgery. It may be indicated for hyperkinetic children and for extensive surgery in a small child (e.g. correction of malalignment). For rapid and minor surgery, sedation with nitrous oxide should be the first choice when available [48].

Nail avulsion

Indications

Nail avulsion is the most basic procedure in nail surgery and is a prelude to most additional surgical procedures. It allows visualization of the nail bed and matrix, thus allowing good exposure for biopsy or excision (Fig. 22.15a). Total surgical removal should be discouraged because, as the counterpressure exerted by the nail plate disappears, the distal wall and pulp rise upward giving rise to a bulky digital tip, increasing the risk of distal embedding during nail regrowth [8] (Fig. 22.15b). Partial nail avulsion should always be preferred [49]. Partial avulsion serves as an adjuvant treatment in onychomycosis as it reduces the fungal mass (Fig. 22.15c,d), is a part of the procedure for chemical matricectomy in ingrowing toenails (see “Ingrowing toenails”), may be performed to drain an acute paronychia, and is essential to explore pigmented lesions within the nail matrix.

Procedures

There are two approaches to nail avulsion: distal and proximal, although the latter is less frequently used.

Distal nail plate avulsion starts with the introduction of an elevator under the PNF, moving back and forth from one side to another to detach the fold from the plate. The elevator is then inserted under the free edge of the nail plate in a distal to proximal direction to free the plate from its bed. As the instrument reaches the matrix area where the attachment of the nail plate is looser, a decrease in resistance is felt. The instrument should be inserted from the hyponychium several times back and forth, but never in lateral movements across the nail bed to loosen the nail plate, to avoid injuring the fragile longitudinal nail bed ridges. Caution must be taken to fully detach the lateral horns of the nail plate. The plate is then grasped by a hemostat on one lateral edge and avulsed in a rotating motion (Fig. 22.16a) Another option, if the proximal matrix area is not to be explored, is the trap door avulsion: the nail plate is lifted like a hood (Fig. 22.16b) and not avulsed laterally. This allows surgery on the bed and distal matrix [50]. If the avulsion is being performed to explore the whole matrix area, avulsion alone will not suffice. Two releasing incisions, about 1 cm in length, are made at the junction of the proximal and lateral nail folds and angling laterally and proximally. These allow the nail fold to be reflected so that the matrix can be inspected. Skin hooks or sutures may help to maintain the reflection of the PNF during biopsy or excisional surgery (Fig. 22.16c). At the end of the procedure, the fold is put back in place and secured with simple interrupted sutures or adhesive sutures. The nail plate should be repositioned to cover and protect the wound during the early stages of the healing process. It can be secured by stitches or adhesive sutures. It will not reattach and will eventually be shed, but provides protection and minimizes discomfort in the immediate postoperative period.

Proximal nail avulsion is advised when the distal subungual area strongly adheres to the nail plate (e.g. in thick hyperkeratosis) and it is then difficult to find a cleavage plane between the plate and the bed. The PNF is
Figure 22.15  (a) Total lateral avulsion revealing a tumor on the nail bed. (b) Distal embedding resulting from complete avulsion. (c) Onychomycosis presenting as a yellow streak. (d) Partial avulsion.

Figure 22.16  (a) Sequence of distal nail avulsion. (b) Trap door avulsion. (c) Skin hooks allow reflection of the proximal nail fold. (d) Sequence of proximal nail avulsion.
detached as described previously. The elevator then reflects the PNF and is delicately inserted under the base of the nail plate where the adherence to the matrix is weak. The procedure is repeated along the whole width of the nail root. The avulsion progresses distally following the natural cleavage plane up to the hyponychium (Fig. 22.16d).

**Partial nail avulsion** is performed in the same way to the distal approach, but restricted to a portion of the nail plate [49]. For exposure of the matrix area, avulsion of the proximal third of the nail plate is best. It starts with two lateral incisions on the PNF at 45° allowing it to be reflected. A jaw of a nail splitter is inserted under the lateral border of the nail plate, approximately 5 mm distally to the lunula. The plate is cut horizontally to the other side. A hemostat grasps the lateral portion of the plate and lifts it up laterally, as for a sardine box, exposing the whole matrix area (Fig. 22.17a). After surgery, the plate is laid back in place and sutured to the lateral fold. All variants are possible to expose only the area that the surgeon wants to explore (Fig. 22.17b).

**Biopsy of the nail area**

Biopsy of the nail area is almost as simple as at any other site and it is a very useful procedure.

**Indications**

The reasons are similar to those for performing skin biopsies:

- to make a clinical diagnosis
- to confirm a clinical diagnosis before prescribing systemic treatment (steroids, retinoids, ciclosporin)
- to aid in the diagnosis of dystrophies limited to the nail apparatus, such as lichen planus or psoriasis

**Figure 22.17** (a) Proximal avulsion exposing the whole matrical area. (b) Various types of partial avulsion. Adapted from Abimelec and Dumontier [7] with permission of Elsevier.
● to establish early diagnosis of malignant subungual and periungual neoplasia or to facilitate the diagnosis of certain benign tumors
● to discover previously unknown diseases.

Procedures
Surgical procedures obey rules to minimize scarring and offer the best functional and cosmetic outcome as well as sufficient and adequate material for the pathologist. The nail plate is a hard structure and it requires some force to cut through it, especially when it is thickened from some disease. Before surgery the digit should be soaked for about 10 min in antiseptic solution or even saline solution to soften the nail plate. Another option is to ask the patient to soften the nail by nightly application of a 30–40% urea paste for three to four nights prior to surgery.

In the nail bed, incision lines should be oriented longitudinally, whereas in the matrix they should ideally be carried horizontally (Fig. 22.18).

The techniques used for nail biopsy depend upon the location of the pathology within the nail unit.

Nail bed biopsy
Nail bed biopsy is a simple and safe technique that facilitates the diagnosis of a variety of nail bed disorders. Indications are diseases of the nail bed presenting as onycholysis, subungual hyperkeratosis, or a tumor of the nail bed.

If the nail is detached from its bed, the plate is clipped away to visualize the area to be biopsied. In the absence of onycholysis, a partial or total nail avulsion will expose the area to be biopsied. Partial nail plate avulsion is more elegant, less invasive, and sufficient to allow adequate sampling for histological diagnosis in most cases [10]. As for the skin, an incisional biopsy is performed with a punch and an excisional biopsy with a blade.

The punch is pushed, perpendicular to the surface of the bed, in a rotating motion until hitting the bone (Fig. 22.19a). Sharp-pointed scissors (Graddle and LaGrange) are gently inserted at the level of the periosteum to release the specimen [10]. Forceps should never be used as the fragile specimen may be crushed between the jaws. The specimen, once snipped, should only be harvested with gauze or with the scissor tips. Bleeding is minimal and may be stopped with hemostatic solution. If it is not, a piece of hemostatic foam may be pushed into the defect. No suture is required, as a defect up to 4 mm will heal by secondary intention without any dystrophy. Another elegant way of punching the bed in the absence of onycholysis is the double-set punch technique [52] (Fig. 22.19b). A 6 mm punch is made through the plate only. The disk of keratin is removed with the tip of a no. 11 blade and a smaller punch of 3 mm is performed on the nail bed down to the underlying bone. The enlarged hole in the plate overcomes the difficulty in harvesting the biopsy material from a narrow window in the nail plate. The keratin disk may be replaced and secured with adhesive strips and will act as a dressing. If the plate is needed for histology, the hole is filled with hemostatic foam.

Elliptical biopsy of the nail bed is indicated to remove larger specimens (e.g. small tumors). The elliptical excision should always be orientated in the longitudinal axis. The specimen is detached from the bone with sharp-pointed scissors or with a blade (Beaver blades are particularly useful). As the bed has no laxity at all, it is mandatory to undermine the edges of the ellipse: the blade, resting flat on the bone, is gently slid laterally under the edges of the wound. This lateral undermining of the edges should be generous. It usually allows primary closure of the defect with 4/0 or 5/0 absorbable sutures. Pulling on the lateral edges may tear the bed. Reapproximation is sufficient and the small remaining defect will close by secondary intention.

Matrix biopsy
Matrix biopsies are most interesting for longitudinal melanonychias (LM). An accurate histological examination requires examination of the entire pigmented lesion, therefore incisional biopsies are not recommended and only excisional biopsies should be performed. Dystrophic sequelae are unlikely if the pigment rests within the distal matrix, as the latter synthesizes the ventral part of the nail plate. The only consequence will be a nail plate thinned from below. Fortunately, LM originate in the distal matrix in 85% of cases [53]. If the pigment is located or extends within the proximal matrix, nail plate dystrophy is highly probable, as this part of the matrix generates the upper third of the nail plate. Several techniques are available according to the width and shape of the band. Each of the following procedures starts identically with exposure of

Figure 22.18 Orientation of biopsies at the nail apparatus.
the whole matrix (see “Nail avulsion”). However, if the LM is very pale, it might be judicious to punch the origin of the LM before avulsing: proximal avulsion tears off the superficial layers of the matrix epithelium and the origin of the band may become hardly visible after avulsion. Thanks to the punching, the area to harvest is obvious after proximal avulsion [54] (Fig. 22.19c). If the band is heavily pigmented, there is no need to go through this phase. All procedures end in the same manner: the nail plate is laid back in place and secured to the lateral nail fold. The PNF is released and the two lateral incisions may be sutured (this is interesting only for hemostatic purposes) or secured with adhesive strips.

- If the pigment has a round shape, is less than 3 mm, and is located in the distal matrix, the punch biopsy technique is best [55]. A 3 mm punch, containing the whole pigmented macula, is pushed vertically into the matrix, down to the bone (Fig. 22.20a–c). Without using forceps, which tend to crush the fragile matrix tissue, fine-tipped scissors, preferably curved, are inserted vertically around the specimen and delicately sever the specimen cylinder at the level of the periosteum. The scissor tips gently lift and remove the specimen without crushing it. The defect is left open.

- If the pigment has a longitudinal shape, an elliptical excision is indicated [54]. The pigmented source is removed in a longitudinal ellipse with minimal margins. The specimen is detached from the underlying periosteum using fine-tipped scissors. It should never be handled with forceps at any time and only harvested with the tip of curved scissors (Fig. 22.21a–c). Undermine generously (at least 5 mm) each side of the incision with a no. 15 blade. Reapproximate the edges of the defect with 5/0 or 6/0 absorbable sutures. Biting at least 3 mm laterally and not pulling on the stitches avoids tearing the fragile matrix.

- If the pigment involves a wide area of the matrix, tangential excision is indicated. This technique virtually “shaves” the matrix [56]. It removes the matrix epidermis and only a small layer of dermis. A shallow incision is carried out around the pigmented zone. The scalpel (ideally with a Teflon-coated blade) is then held horizontally and with sawing motions the lesion is

---

Figure 22.19 (a) Punch biopsy of the nail bed. The device is pushed vertically until bone contact. (b) Sequence of the double-set punch biopsy. (c) Punching through the nail at the origin of a pale longitudinal melanonychia before proximal avulsion. Courtesy of S. Goettmann.
removed from the deep dermis (Fig. 22.22a–c). This is a difficult procedure. The thickness of the surgical specimen is such that the scalpel blade is seen shining through it; it should not be thicker than 0.5 mm [57]. The specimen is placed on filter paper and properly oriented for the pathologist. If not delivered properly to the laboratory, it will curl like cigarette paper in the formaldehyde jar and cannot be processed (see “Handling biopsy specimens”). It allows the pathologist to have a look at the entire lesion; however the margins are...
difficult to assess. It has been shown to provide adequate slides and allow an accurate diagnosis in all cases. No postoperative dystrophy was noted even if almost all the distal matrix had been removed. When the proximal matrix was concerned, it resulted in nail thinning and brittleness in most cases and exceptionally in pterygium. Its main drawback is a recurrence of the pigmentation in about three-quarters of cases [58]. This technique avoids mutilating surgery in cases of benign large LM.

Lateral longitudinal nail biopsy
This procedure allows the study of the whole nail apparatus: PNF, matrix, nail bed, nail plate, and hyponychium. It is indicated in:

- inflammatory disorders with alteration of the surface of the nail plate resulting from involvement of the proximal matrix
- excision of tumors located in the lateral third of the plate
- excision of LM affecting the lateral part of the plate.

It is mostly interesting in the case of a disease of the proximal part of the nail apparatus presenting as alterations of the surface of the nail plate or for inflammatory conditions in which all these structures are involved concurrently. However, it is mandatory that at least one nail exhibits lateral involvement with marked clinical signs to denote pertinent histological alterations. The patient must be informed that this type of biopsy will narrow the nail permanently due to the partial amputation of the lateral horn of the matrix. All incisions are carried down to bone contact. The specimen should not exceed 3 mm in width in order to avoid any postoperative lateral deviation [59]. The lateral nail fold should not be included in this type of biopsy. It might be included for tumor removal.

The incision starts halfway between the cuticle and the distal interphalangeal crease and progresses distally through the PNF (where the nail is the softest), the nail plate and its bed, to the hyponychium. It may be hard to cut through the plate: repeated up and down movements with the blade with distal progression (as in cutting a tart) help greatly. Proximally, the incision takes a laterally curved direction that extends about halfway on the lateral aspect of the digit, as far as the distal interphalangeal crease [60]. This is especially mandatory on the great toenail. This allows complete removal of the lateral horn of the matrix and ensures a more anatomical closure at the junction of the proximal and lateral nail folds. A second incision, starting from the distal extremity of the previous one, runs from the hyponychium into the lateral sulcus and joins the proximal end of the previous incision. It parallels the first one, ensuring a sigmoid excision (Fig. 22.23a). The biopsy reaches a width of 3 mm at its widest point. The specimen is then removed distally to proximally. The specimen should be held very cautiously, using delicate forceps (Fig. 22.23b). Using fine, sharp, curved scissors with “tips down” [61], the specimen is detached from the periosteum. At the proximal tip of the biopsy, great care must be taken, as the matrix should be part of the biopsy (Fig. 22.23c), and one should avoid coming up with scissors too soon and foreshortening the specimen [62]. The defect should then be reviewed to avoid leaving small remnants of matrix. Any matrix tissue left in the site will lead to nail spicule formation. The PNF and the hyponychium are closed with simple stitches using 4/0 nylon. A half-buried horizontal mattress suture with 4/0 nylon, starting in the lateral nail fold and going through the nail plate, will recreate a lateral nail fold.

Figure 22.23 (a) Incisions in a lateral longitudinal incision. (b) Harvesting the specimen. (c) Sutures recreating a lateral nail fold.
Proximal nail fold biopsy
Lesions of the nail fold can be biopsied with shave, punch, or incisional techniques or excised en bloc. A Freer elevator should be inserted beneath the PNF to shield the matrix from inadvertent damage from the scalpel. When the indication is similar to a biopsy elsewhere on the skin (e.g. nevus), a punch biopsy (not over 3 mm) may be taken on the PNF, taking care that its distal margin is always preserved.

For biopsy of collagen diseases more tissue is required. A crescent-shaped excision, 2–3 mm wide, is carried out from one side to the other, removing the distal PNF en bloc. This amount of tissue allows histology, immunohistochemistry, and electron microscopy to be performed [63]. Healing by secondary intention is very rapid (less than 4 weeks). The cosmetic outcome is excellent, with only more of the nail plate and lunula visible. The procedure may be used for recalcitrant chronic paronychia [64] and for removal of tumors located in the distal PNF.

Handling biopsy specimens (Beth Ruben)
Once obtained, it is crucial that the specimen be handled optimally from that point to ensure the best chance for accurate diagnosis. Many pathology laboratories are unfamiliar with submitting nail unit tissue for processing and this element should not be left to chance. Therefore, the surgeon should communicate clearly with the pathologist to ensure that it is handled correctly. Explicit instructions about any special orientation needed are essential. It can also be helpful to instruct gross room personnel to ask a pathologist about any nail specimen before submission, with such a request included on the requisition form. The surgeon should also specify what part of the nail unit has been sampled; for example, nail matrix, bed, or perhaps a longitudinal sample of the nail unit. With respect to submission of specific specimen types, punch biopsies of the nail matrix or bed can be submitted without much problem. If there is any indication that it might be difficult to discern the surface of the punch after processing, one could consider putting the specimen between sponges in a cassette in the proper orientation (surface up for example) and placing the cassette in formalin. For tangential shave biopsies, special handling is often needed to ensure proper orientation and to prevent curling. To assist with this, the specimen can be placed on a piece of paper, cardboard, or nail unit template (Fig. 22.24a,b), and the paper can be marked with ink to indicate proximal or distal, so that the specimen is sectioned longitudinally by convention, if sectioning is required. Inking small specimens can be difficult (the ink may travel over the specimen indiscriminately) and thus should be avoided. In addition, ink may interfere with microscopy, especially black ink in the case of melanocytic proliferations. Longitudinal biopsies of the nail unit may be obviously oriented based on landmarks such as the PNF, but if they are not full length, orientation can be provided. In this case, a small amount of ink can be placed at the distal aspect and a template can also be used, or a simple diagram drawn on the requisition form. Whole nail unit excisions again are usually naturally oriented. Nail unit specimens are sectioned longitudinally by convention as this makes it easier to see important landmarks in their natural orientation. When there are separate samples of nail plate and a soft tissue specimen, such as underlying matrix, these should be submitted in separate specimen bottles and maintained in separate cassettes during processing. Problems can arise with embedding and sectioning if they are placed together. Formalin fixation is standard for nail specimens. They may require softening agents in the laboratory but strong acids should be avoided. More details with respect to nail unit processing techniques can also be found in Chapter 1.

Closures of defects at the nail apparatus
This section will deal with closures of defects at the nail apparatus after removal of a tumor, benign or malignant. Several options are possible for the surgeon; they will depend upon the size of the defect, its location, the surgical skills of the operator, and also the wishes of the patient (e.g. graft versus secondary intention healing). As for skin surgery, closure may be obtained by first or second intention, flap, or grafts. The skin reservoir is almost nil on the finger and one should look for skin in the immediate vicinity of the defect or sometimes further afield (another finger, the palm, the arm). Mobilization of the skin is mainly possible laterally (lateral folds and
pulp) and in an anteroposterior direction only in the area of the hyponychium. The decision is best made on a case-to-case basis, with palpation, manipulation of the nail unit tissues, and evaluation of the patient’s overall health status [65].

On the hyponychium

The distal wall is covered by normal glabrous skin over a fatty cushion protecting the distal tuft of the phalanx. This area is quite flexible and allows good closure in many situations. Due to the extensive mobility of the distal wall on the deep structures, secondary intention healing is not usually indicated. Incisions should be oriented horizontally as much as possible. For small defects, primary closure is easiest as some laxity exists both laterally and vertically. To avoid excess traction on the edges of the defect, relaxing incisions in the pulp are a good option. They will heal very quickly by secondary intention. For a defect located in the distal groove, an A to T advancement flap (Fig. 22.25) is a good choice to avoid an incision in the onychodermal band. In infants, a hypertrophic lip not responding to conservative treatment may be shaved away with excellent cosmetic results (Fig. 22.26a–c).

On the proximal nail fold

The PNF is an excellent location for healing by secondary intention. Small tumors on the distal PNF, such as pseudomyxoid cysts [66, 67], may be excised en bloc and left to heal by secondary intention (Fig. 22.27a–c).

**Figure 22.25** A to T flap in the distal groove.

(a) (b) (c)

**Figure 22.26** (a) Severe hypertrophic distal fold in a toddler. (b) Tangential excision of the hypertrophic tissue. (c) Two years follow-up.

(a) (b) (c)

**Figure 22.27** (a) Myxoid pseudocyst of the most distal part of proximal fold. (b) Drawing of the excision. (c) Immediately post excision.
This technique is derived from the surgery for chronic paronychia described by Baran and Bureau [68]: an elevator is inserted under the PNF to detach the PNF from the nail plate and to protect the matrix resting under the very thin nail plate in the most proximal part of the nail pocket. The PNF is excised in a crescent shaped on its whole thickness, 5 mm in its maximum width, extending from one lateral nail fold to the other. The incision should take away the 5 most proximal millimeters of the lateral nail folds. Healing is fast: epithelialization occurs in 10 days and the cuticle regrows and attaches to the nail plate in less than 2 months. The nail plate dystrophy is replaced by normal nail plate with nail growth. The drawback of this technique is that the PNF is usually slightly shortened, giving rise to a longer nail (more lunula is visible). To avoid this, some authors proposed fully reflect the PNF, removing its fibrous undersurface, and suturing it back in its original position [69].

The defect resulting from a wedge excision in the median part of the PNF may be reconstructed with bilateral advancement flaps. When the defect is not too wide, two relaxing incisions are carried out at both sides of the PNF in prolongation of the margin of the lateral nail folds, thus forming two narrow flaps. They are moved towards each other and sutured in the center (Fig. 22.28a). The two secondary defects are each about one half of the original defect wide and are left to heal by secondary intention, which is usually complete within 10 –15 days.

When the defect from tumor excision is too wide to allow narrow flaps to survive, two small rotation flaps are designed [70]. A curved incision is made from the junction of the lateral with the PNF in the direction of the lateral aspect of the distal interphalangeal joint. Where the flap is lateral to the nail pocket, a horizontal incision is made to allow the flap to be dissected from the lateral aspect of the PNF. Both flaps are rotated towards each other and sutured in the center (Fig. 22.28b). The resulting two crescentic secondary defects may be reduced with one or two sutures or just left for healing by secondary intention.

When the defect is on a lateral side of the PNF, the wedge may be closed in an analogous manner with one incision performed on the other side of the PNF to free the flap (Fig. 22.28c). Again, depending on the width of the defect, the flap may be formed as a simple narrow transposition or a wider rotation flap. When there is still skin lacking, a relaxing incision on the lateral aspect of the distal phalanx and formation of a bridge flap may help to close the defect primarily.

Figure 22.28 (a) Resection of a small median tumor on the proximal nail fold. (b) Resection of a larger median tumor on the proximal nail fold. (c) Resection of a lateral tumor on the proximal nail fold. (d) Full-thickness skin graft for a large defect on the proximal fold.
For large defects not affecting the free margin of the PNF, closure is best performed with a full-thickness skin graft (Fig. 22.28d) to avoid retraction. This can be comfortably taken from the inner aspect of the forearm or upper arm for fingers or the inner aspect of the thigh for toes.

For all these flaps, as in any other location, the risk is necrosis. This event is extremely rare at this site as the PNF is extensively irrigated by two rich vascular arcades (see Chapter 1).

On the lateral nail folds

Small defects are closed easily with primary closure. If this is impossible, the surgeon has to utilize the pulp reservoir with a bipedicled lateral nail fold flap. An incision is made in the mid-lateral line and the flap undermined, while retaining proximal and distal attachments (bridge flap). The flap is freed by inserting fine-pointed scissors in the excisional defect and pushing down and laterally to emerge within the relaxing incision. The primary defect is closed easily without tension and the secondary defect created is left to heal by secondary intention (Fig. 22.29). Necrosis of the flap is exceptional but beware of heavy smokers and patients with impaired vascular flow at the extremities. No dystrophy or retraction is observed at this location as the defect remains of small size.

Large lateral nail fold defects should not frighten the less experienced nail surgeon. See the section “Ingrowing toenails” for how the super U and Vandenbos’ procedures remove very hypertrophic lateral folds and leave them to heal by secondary intention with excellent cosmetic results. The only drawback is the healing time.

On the perionychium

When the defect involves a large part of the folds, the only option is a full-thickness skin graft. The shape of the defect is carefully copied on to a paper or gauze template. The easiest and best placed donor site is the inner aspect of the ipsilateral arm or the inner aspect of the wrist. The skin there is thin, not photodamaged, and hairless in most individuals. It fits very nicely with the skin of the finger. The graft should not be over-defatted to offer some padding. Techniques/complications are the same as for any other skin graft. The results are often extremely good (Fig. 22.30).
On the nail bed

The nail bed regenerates very easily [71] and because nail dystrophies are very unlikely after excision, the nail surgeon should not be afraid of working on it. If the defect is less than 4 mm wide, secondary intention healing is an excellent option. If the defect is larger than 4 mm, there is a possible risk of residual onycholysis and the defect should be closed. Sometimes, a longitudinal lateral relaxing incision may suffice, but in most instances, the defect has to be closed by two lateral bridge flaps. Two longitudinal incisions parallel to the defect are performed, about 4–5 mm lateral to each margin. These two flaps are freed by sliding the scalpel blade under the bed and using gentle back and forth movements until the flaps are completely freed. The defect is reapproximated with 5/0 or 6/0 absorbable sutures. The lateral defect will heal by secondary intention (Fig. 22.31). The plate should always be replaced after nail bed surgery. It serves as a protective, biological dressing, promoting healing and decreasing postoperative morbidity. It is theorized that scant nail bed and matrix keratinocytes that adhere to the ventral avulsed plate act as a partial split-thickness skin graft on plate replacement, accelerating healing [49, 72]. The patient is asked to secure the plate with adhesive tape and to keep it in place as long as possible. When the nail is shed, complete healing of the bed has already occurred and a new nail has grown of about one-third of its length. The scar in the bed may appear as a longitudinal leukonychia or erythronychia.

On the matrix

The matrix sutures easily and can be freed from its deep connective tissue attachments to allow significant movement with simple undermining, contrary to the fibrous nail bed that tears easily when suturing [65]. Small defects in the distal matrix (e.g. punch biopsy) are left to heal by secondary intention, elliptical distal defects are closed primarily with 5/0 or 6/0 absorbable sutures. They will never result in a split nail but rather in a longitudinal erythronychia [73]. Excisional surgery, especially when full thickness, leaves a matrix defect that risks nail splitting if not surgically repaired. This is especially true for proximal and mid matrix defects as opposed to distal matrix defects. Therefore, every attempt should be made...
to meticulously realign the matrix epithelium when the proximal and mid matrix are involved. Narrow defects less than 3 mm wide can usually be repaired primarily as long as the lateral edges of the defect are widely and sharply undermined above the dorsal phalanx. Defects wider than 3 mm are difficult to close. Collins and colleagues designed three elegant sliding flaps that address mainly midline or slightly paramedian defects [74]. These excisions are interesting as they offer sufficient depth, but they have been now overtaken by the tangential excision that offers enough matrix tissue for microscopic examination and leaves no scarring.

**Partial amputation of the nail unit**

Partial lateral ablation of the nail unit, up to one-half, should be covered with a bridge flap from the pulp (see "On the lateral nail folds"). If the defect leaves less than a half, it is wiser to remove the whole nail apparatus, as the very narrow remnant of nail plate is useless and cosmetically unsightly.

The Schernberg and Amiel flap [75, 76] addresses reconstruction of a midline or paramedian longitudinal defect involving all sections of the nail unit. This type of surgery was initially designed for the removal of a wide longitudinal melanonychia [77]. It invariably ends with a split nail, even with the most meticulous surgical design and repair (Fig. 22.32). It has almost disappeared from the nail reconstruction repertoire since the widespread use of the matrix tangential excision. It remains, however, a possible reconstruction in rare cases (e.g. in situ epidermoid carcinoma presenting as a longitudinal erythronychia, scar). The flap is cut from the distal end of the defect on the hyponychium and fingertip, and is prolonged on both sides, parallel to the lateral nail sulcus, 6 mm laterally, until the junction of the proximal to lateral nail fold. Here, it is mandatory to curve the incision line down and laterally to reach about the midline of the lateral aspect of the finger/toe, as the lateral horn of the matrix may extend that low, especially on the great toenail. This will avoid any spicule formation or recurrence of the tumor. The two lateral incision lines join with a transverse cut over the distal interphalangeal joint. The nail bed is dissected from the bony phalanx with sharp scissors or a blade, progressing proximally and sticking to the bone surface. The periosteum should ideally be removed during the procedure. Elevation of the bed is difficult as the unit bed and plate is inflexible. In the matrix area, the surgeon should detach the whole matrix from the bone, especially laterally. When the whole matrix area is fully detached, lifting of the whole nail apparatus becomes very easy. The dissection continues proximally until it reaches the most proximal incision over the distal interphalangeal joint. Care must be taken to prevent a distal extensor tendon injury. This event remains extremely rare as this structure is hard and easily recognizable with its shiny whitish structure. However, in elderly patients this structure may be fragile and more easily damaged. The remaining attachments are cut transversely with scissors. At the end of the procedure the bone should be naked, giving rise to the term skeletization (Fig. 22.33). A running locked suture is performed all around the defect for hemostatic purposes.

Closure of the defect is obtained either by secondary intention, skin grafting, or cross-finger flap. Secondary intention healing is preferred on toes, as footwear may impair the survival of a graft. If proper care is performed and the patient is in general good health, healing will take from 4 to 8 weeks (Fig. 22.34). Retraction

![Figure 22.32](image_url) (a) Schernberg and Amiel flap. (b) The flap is vascularized by the branches of the medial phalangeal artery.
Nail Surgery

is a common phenomenon and may be responsible for traction scars that may be uncomfortable. Repeated massaging and silicone dressings help greatly.

*For skin grafting*, selection of the donor site should take into account minimal functional impairment from the removal of tissue and maximal hiding of the scar as well as the proximity to the recipient site [7]. It is obvious that the area should be as hairless as possible. Therefore, the preferred site is the inner aspect of the ipsilateral arm. Other options are the groin, the gluteal folds, and the lateral side of the trunk. An exact pattern of the defect should be transferred on to filter paper or gauze to design the graft in the donor area. The graft should be gently defatted, but not excessively, in order to keep some padding to avoid the graft adhering to the bone, which may be painful during everyday activities.

Suturing the edges of the graft to the borders of the defect should be performed very carefully and slightly evensant. Functional results are very good as almost normal distal interphalangeal joint mobility and sensory discrimination are achieved (Fig. 22.35). However, patients may experience some difficulty with precise handling (e.g. fastening buttons) that varies according to the finger operated on. Patients are mostly satisfied with the cosmetic appearance: full-thickness grafts often go unnoticed by a non-informed audience and are often forgotten by the patients themselves. Implantation cysts have been reported as the main complication [80].

*A cross-finger flap* is a valuable option when neither another flap nor a full-thickness graft is feasible. It is a more demanding, three-stage technique to repair a full-thickness defect of a digit, particularly the dorsal aspect of the tip of a finger. The critical part of a cross-finger flap is designing the flap before raising it completely and

![Figure 22.33 Resection en bloc of the nail unit: skeletization.](image)

![Figure 22.34 Secondary intention healing on the great toenail. The whole process took 10 weeks.](image)

![Figure 22.35 Full-thickness skin graft. Aspect at 6 months.](image)
transposing it to the defect. Another 18–20 days are necessary for the flap to heal before its pedicle is severed. Usually the volar skin of the middle phalanx of an adjacent finger is used (Fig. 22.36), except for the thumb where the volar skin of the proximal phalanx of the index finger is used [81, 82].

**Microscopically controlled surgery**

Microscopically controlled surgery, also called micrographic surgery or Mohs surgery, is a technique of tumor removal that enables immediate three-dimensional margin control. Originally performed after in vivo fixation of the suspicious tissue with 50% zinc chloride paste and excision of the fixed tissue layer by layer, this very painful procedure has now been abandoned and is performed as the so-called fresh tissue technique. Mohs surgery of the nail unit requires some particular technical considerations [83].

**Indications**

Indications for Mohs surgery of the nail unit are all ill-defined tumors and tumor recurrences [84].

**Procedure** (Fig. 22.37a–d)

The tumor is outlined and its excision line with a narrow safety margin is drawn on the skin. Exuberant tumors are debulked by curettage or tangential removal; this also permits the clinical diagnosis to be confirmed histopathologically. The first excision is carried along this line and the surgical specimen is meticulously marked with different colored inks to locate exactly each particular point of the specimen’s circumference. This is drawn on a map of the nail unit for proper orientation in the histopathology laboratory. The specimen is cut tangentially in order to include the entire surgical margin in the histological section. This requires tissue that can be laid flat on the chuck of the cryostat, which is easy for small excisions of normal skin, but may be challenging for excisions from the nail because of their anatomy.

We have adopted a step-wise technique that can be adapted for tumors on the PNF, at its undersurface, in the matrix and the nail bed, as well as the entire nail unit (Fig. 22.37a). The surgical anatomy of the nail unit as seen in dorsal view and a sagittal section of the distal digital phalanx is shown in Fig. 22.37a. This is also adequate for neoplasms on one side of the nail unit.

A presumed tumor on the PNF is shown in Fig. 22.37b. The entire PNF or a segment of it is removed by separating it from the underlying nail plate and sectioning further proximal to the joint crease parallel to the level of the nail. The proximal as well as the two lateral margins are marked with different colored inks. The cuticle does not need color marking as it is easily seen histologically. The entire tissue block is frozen on a glass slide so that the cut surfaces form one even plane that is then cut with the microtome from the deep to the superficial portion of the specimen.

A tumor of the ventral surface of the proximal nail is treated in the same way in case it does not reach the apical matrix (Fig. 22.37b). However, when the proximal matrix is reached, a more extensive excision is necessary (Fig. 22.37c). The excision lines are drawn on the dorsal surface of the PNF. It is separated from the underlying nail and the proximal third to one-half of the plate is avulsed. It cannot be left in place as its curvature prevents flattening of the surgical specimen and thus getting

Figure 22.36 Cross‐finger flap for a defect of the thumb nail.
Figure 22.37 Sequence of Mohs surgery at the nail unit. (a) Tumor of the dorsal surface of the proximal nail fold. (b) Tumor of the ventral surface of the proximal nail fold. (c) Tumor of the apical matrix. (d) Tumor involving the matrix and nail bed or the entire nail apparatus. C, cuticle; DIP, distal interphalangeal joint; DP, distal phalangeal bone; ET, extensor tendon; HO, hyponychium; L, lunula; M, matrix; NB, nail bed; NP, nail plate; PNF, proximal nail fold.
Figure 22.37 (Continued)
Nail Surgery

the complete undersurface in one section. The excision is carried down to the bone and the dorsal interphalangeal joint aponeuroses to remove the proximal portion of the nail unit. This surgery may be done in two steps in case it is not certain whether the proximal matrix has been reached or not. In this case, the first step is as shown for tumor localization on the dorsal surface of the PNF and, if there is margin involvement, the procedure is completed as described in a second step.

A tumor involving the matrix and distal nail bed is excised in an analogous way (Fig. 22.37d). The first excision is performed as in Fig. 22.37b. Then the nail plate is avulsed and the proximal two-thirds of the nail unit including the proximal half of the nail bed and entire matrix proximal to the interphalangeal joint are dissected from the underlying bone with or without the periosteum of the dorsal aspect of the terminal phalanx. In the case of an ungual melanoma, a 6 mm safety margin is planned around the anatomical borders of the nail apparatus. If there is a Hutchinson's sign, we recommend a 10 mm margin as so-called field cells have been found in the epidermis up to 9 mm from the visible border [85].

**Ingrown toenails**

Ingrown nails are commonplace, occur at any age though with variable frequency, are mostly seen on the great toe and may interfere considerably with normal daily activities through the discomfort, pain, and inflammation that they usually cause.

The etiology of ingrown nails is still debated; probably most cases are due to too wide a nail compared to the width of the nail bed, whereas in some cases there may be hypertrophy of the lateral nail folds. According to the assumed etiology, when the nail is primarily at fault, the condition is termed ingrowing or ingrown nail, whereas those who believe that the nail fold is the reason tend to call it onychocryptosis. The list of presumed causes and precipitating factors is long: improper nail trimming with cutting away of the distal lateral nail edge(s) usually leaves tiny spicules and also allows the tip of the toe to be compressed so that when the nail regrows, the spicules pierce the soft tissue. In some exceptional instances, the spur will grow distally and run through the distolateral wall to finally emerge at the hyponychium. This form is called “harpoon nail” (Fig. 22.38a,b) [86]. This may be aggravated by tight, pointed high-heeled shoes, tight socks, foot deformation, congenital factors, hyperhidrosis, the juvenile type of diabetes mellitus, and even some dermatological conditions [87, 88]. Baran classified ingrowing toenails into different categories long ago, suggesting that each type may benefit from a specific treatment [89]. Surgical treatment of ingrown toenails is indicated either when conservative treatments have failed or when the condition is extremely painful or recurrent and the patient asks for a radical solution.

Depending on the age of the patient, different types of ingrowing nails are seen (Table 22.1).

There is no “cure-all” technique for ingrown toenails. Two different approaches are mainly used: narrowing the plate or debulking the soft tissues. These approaches are available to all types of nail surgeons from beginners to experienced. All the procedures cited in the following paragraphs have high cure rates as long as they are properly performed. As with all surgical procedures,
they are operator dependent. Chemical cautery is the easiest and most versatile technique and may help in almost all instances of lateral ingrowing and pincer nails. For distal embedding and very hypertrophic and exuberant lateral folds, debulking with healing by secondary intention is the most effective and easy to perform, giving excellent results.

Conservative treatments

Physicians favoring non-invasive treatments consider the etiopathogenesis of ingrowing nails to be due to a condition amenable to protection of the lateral nail fold from the offending distal nail edge. There are several different methods to achieve this goal, all of which require excellent patient compliance.

**Taping** is the least aggressive method. It is performed with one or several layers of adhesive tape that is wrapped around the involved nail fold to pull it away from the nail (Fig. 22.39a,b). Care should be taken to avoid circular taping in order to avoid strangulating the toe. This method is often helpful in mild cases. Education of the patient on how to perform it is mandatory. The tape may not stick sufficiently to the skin when there is oozing and too much granulation tissue. For the same reason, profuse sweating, often observed in teenagers, does not allow this procedure. Creams cannot be used, but foot baths to reduce inflammation and oozing are recommended once or twice a day. The pain disappears very rapidly. Taping should be continued until the offending corner of the nail has completely grown out. No further manipulation must be carried out [90].

**Packing** is the method by which a wisp of cotton or non-adhesive impregnated gauze is inserted between the nail corner and the nail groove. This may be uncomfortable the first few times but as soon as the material is in place the pain virtually disappears. Again, the packing has to be continued until there is full outgrowth of the nail edges. Whether the cotton is replaced every day or left in place for some days depends on the severity of symptoms and the ease with which the patient can manage this procedure. Once the oozing has stopped, the cotton may be fixed with a bit of acrylic glue and left in place for a week or two. It then becomes rigid and has been called a “cotton nail cast” [91].

**Dental floss** has been used instead of cotton and was claimed to have been successful and easy to apply [92].

Application of an artificial acrylic nail on broken nails is another useful and sometimes efficacious method. The defective nail is repaired in such a manner

<table>
<thead>
<tr>
<th>Table 22.1 Different types of ingrowing nails.</th>
</tr>
</thead>
<tbody>
<tr>
<td>Neonates</td>
</tr>
<tr>
<td>Infants</td>
</tr>
<tr>
<td></td>
</tr>
<tr>
<td>Juvenile</td>
</tr>
<tr>
<td>Adults</td>
</tr>
<tr>
<td>Distal embedding</td>
</tr>
<tr>
<td>Pincer nails</td>
</tr>
<tr>
<td>Retronychia</td>
</tr>
</tbody>
</table>

(a) (b)

Figure 22.39 Conservative treatment: taping. (a) Before the procedure. (b) Once placed, the taping pulls the lateral fold away from the plate.
that the entire nail bed is covered with a thick nail with round margins that will not pierce the soft tissue [93] (Fig. 22.40).

Gutter treatment is a semiconservative method as it requires local anesthesia. The ingrown lateral margin is freed and a piece of a small plastic tube, for instance from an infusion set, that has been cut lengthwise, is pushed over it. It gives the lateral margin a broad surface on which the pressure is distributed and the lateral groove is protected from irregularities of the nail margin. The gutter is grasped with a small hemostat clamp and moved into the nail groove and over the nail margin. This is then dried and fixed with acrylic glue or alternatively with two or three stitches or adhesive tape. The gutter is left in place until it has grown out with the nail [94].

Unbending of the nail is another principle of conservative ingrown nail treatment. The easiest method is to use braces that can be adapted over the course of weeks and months to achieve the result required. It is the chief therapy for pincer nails but may also be applied to the juvenile type of ingrown nail if it is associated with a marked transverse curvature [95, 96]. Pain relief and flattening is obtained in almost 100% of the cases in a 3-month period [97]. The most common braces are made from steel wire. They may have a spring that exerts an anticonvex power when hooked under both nail margins, or the power can be adapted by turning a loop in the wire. There are also elastic plastic bands that can be glued on to the overcurved nail. Another technique uses elastic wire with only one hook on one side of the nail, the other free end of the wire being glued on to the nail plate. Thinning of the nail plate by grinding longitudinal grooves may help for particularly thick nails. Another technique is the use of 5% thioglycolic acid in conjunction with superelastic wire [98, 99]. The thioglycolic acid, which cleaves the sulfur bridges of nail keratin, softens the nail so that it may then be flattened with superelastic wire. When the glycolic acid ceases working, the newly arranged keratin filaments will be fixed in their corrected position, keeping the flattening action active [100]. It was claimed that flattening of pincer nails was sufficient within 1–5 days in all cases. New devices to open the curvature of pincer nails are clips made from shape memory alloy containing copper, aluminum, and manganese [101]. They require a certain length of the nail as they are stuck on the free nail end, and they cannot be used in nails with considerably more curvature than 180°.

Nail ironing using hot hemostat clamps is another technique to unbend the nail. It also requires a nail long enough to insert the hemostat without burning the patient and it is only applicable in mild cases [94].

The best results are obtained by a combination of packing, taping, acrylic affixed gutter, and braces, superelastic wire, or nail ironing.

Ingrown nails with granulation tissue are always contaminated with bacteria. Hence, many physicians administer
antibiotics for their treatment. Although this may reduce the concomitant inflammation it will never cure an ingrown nail as the bacterial infection is secondary to the offending nail. Disinfectant baths may be advisable before cold-steel surgery.

Hygienic measures, correct nail trimming, and wearing of sufficiently large shoes are needed to maintain the success of all conservative treatments.

**Narrowing the nail plate permanently**

**Chemical cauterization**

Partial chemical matricectomy with 88% phenol (Fig. 22.41) has been performed for more than half a century [102] and is the most commonly used technique by dermatologists [103, 104]. Phenolization is safe both for the patient and the surgeon [105]. Three consecutive Cochrane studies [106–108] demonstrated that phenolization was the most effective technique for definitive treatment in terms of morbidity and success rate, compared with other excisional surgical procedures, in preventing recurrence at 6 months or more. In most large studies the success rate is 95% or more [109, 110]. Phenol has three main properties that are important for both the surgeon and the patient: it is necrotizing, disinfecting, and anesthetic. This allows simultaneous destruction of the tissues where it has been applied, disinfection of the surgical field (allowing one to operate on even moderately infected toenails), and a very comfortable postoperative period for the patient as phenol induces demyelination of the terminal nerve endings for several weeks [111]. After local block, a tourniquet is placed to ensure a completely bloodless field. Granulation tissue, if present, is curetted for a better view of the lateral part of the nail plate, avoiding excessive nail plate removal. A lateral (or bilateral if the condition affects both sides) strip of nail about 3–5 mm is split with nail nippers from the free edge up to the most proximal part of the nail, under the PNF, and avulsed. A cotton swab is soaked in the 88% phenol solution and then cautiously padded on gauze to have it just moistened and not dripping. If there is too much liquid on the cotton-tipped applicator, it will spill onto the nail folds causing unnecessary burning. This is why the first description of the technique recommended protecting the surrounding skin with some greasy ointment. Any overflow should be mopped away immediately with gauze. Excess of cauterant may also slide under the lateral aspect of the nail and induce “overphenolization.” Other applicators may be used for applying the cauterant: orange sticks, urethral swabs, or the elevator itself [18]. Phenol acts by coagulating tissue proteins. A bloodless field is mandatory at this point otherwise phenol will coagulate blood proteins instead of those of the matrix epithelium. This is the most common cause for recurrences. The ideal time of application varies from 2 to 3 min [112]. An interesting histological study on cadavers showed that 4 min may be necessary for complete destruction of the nail matrix down to its basal layer [113]. Curettage of the matrix before applying the cauterant does not increase the success rate [114] and exposes the toe to periostitis with potentially catastrophic consequences [115]. On the contrary, it has been clearly demonstrated that immediate removal of all tissue modified by phenolization, by gentle curettage, dramatically shortens the oozing time from chemical matricectomy [116]. The wound is cleaned with saline solution and dried with sterile gauze. Alcohol lavage does not neutralize the phenol as was thought in the past (the reason why it was named the “phenol–alcohol procedure”). Studies demonstrated that alcohol only dilutes the phenol and drags it partially away [117]. The cauterant will be immediately inactivated when the blood flow returns after release of the tourniquet. The procedure may be performed in diabetics with the same success rate as in non-diabetics [118], in children [119], and in recalcitrant ingrowing from epidermal growth factor receptor (EGFR) inhibitors [120]. The main drawback of the technique is oozing for several weeks (3–6). This may promote infection, especially in patients with poor hygiene [121]. However, with regards to the very large number of phenolizations performed, infection remains very unlikely. Application of 20% ferric chloride after phenolization reduces the

![Figure 22.41 Chemical cauterization for ingrowing toenail.](image-url)
duration of oozing [122]. More recently, it has been shown that using lidocaine with epinephrine for the anesthesia significantly shortens the oozing period [123].

Ten percent sodium hydroxide has also been used as a cauterant for selective matricectomies. Success rates are similar to phenol [124] and postoperative drainage is shorter (average 9 days for sodium hydroxide versus 17 days for phenol). Application time is 1 min [125]. This cauterant is also suitable for diabetics [126] and children [127].

One hundred percent trichloroacetic acid (TCA) was used for matrix cauterization [128, 129]. This showed that TCA matricectomy is a safe, simple, and effective procedure with a success rate similar to that of phenol and sodium hydroxide (95%) but with very quick healing (only 2 weeks). A comparative, prospective, randomized and double blind study demonstrated that the healing time is similar for phenol and TCA. TCA should be considered as a serious alternative, especially when phenol is not available [130].

Chemical cautery is very easy to perform and should be known by all dermatologists. It is indicated in ingrowing toenail stage 2 with or without pyogenic granuloma and in any pincer nails. In the latter, it will immediately relieve the patient from the pinching effect on the underlying tissue. Within the postoperative year, the nail will flatten.

**Wedge excision**

Wedge excisions remain very popular in the orthopedic literature. Several variants have been described under the names of Winograd’s, Zadik’s, or Emmert’s procedures. All of them involve en bloc resection of the lateral part of the nail plate, its corresponding bed, and matrix. Contrary to what one might expect, this is very delicate surgery as complete dissection of the lateral horn from the underlying periosteum is not easy. Skilled nail surgeons may achieve excellent results with this type of surgery [131] as they have perfect knowledge of the anatomical bounds of the lateral horns of the matrix and for this reason curve proximally their incision, as they would do for a lateral longitudinal biopsy [82, 132] (Fig. 22.42). This is the main reason for the various recurrence rates observed in different studies. Pain is the major drawback of the technique, due to the trauma to the periosteum induced by dissection of the adherent matrix. Complications are frequent: (i) a high postoperative infection rate (20%) due to the unique concentration of resident microbes in the nail folds, warranting routine antibiotic prophylaxis [133] – fungal septicemia has even been reported [134]; (ii) lateral deviation when more than 3 mm of the plate is resected [59]; (iii) spicule formation (very common) [135] (Fig. 22.43); (iv) inclusion nail [136]. For all these reasons, wedge excisions are not recommended for ingrowing toenails.

**Lasers**

A lot of publications on laser treatment of ingrowing toenails have been published. Most commonly an ablative CO₂ laser is used. A lateral strip of nail plate is avulsed, either surgically, as for other techniques, or removed...
with the laser beam in a cutting mode. Most authors incise the PNF laterally and recline it to allow full exposure of the lateral horn of the matrix. Here again no blood is tolerated and a tourniquet is mandatory. The lateral matrix horn is vaporized (power and spot size may vary according to personal experience and machine used) and sometimes the corresponding nail bed [137]. Staining the lateral matrix with sterile methylene blue may aid in estimating the degree of matrix ablation [138]. Experienced and skilled laser surgeons may achieve success rates almost as high as those of chemical cautery [139, 140]. The main advantage of the CO2 laser is its hemostatic effect.

Electrocautery
After local anesthesia, a lateral strip of nail is removed and the lateral matrix horn is exposed. Electrocauterization of the matrix is performed in a bloodless field. As a lot of heat is delivered, thermal periostitis with long-term postoperative pain, long healing time, and nail dystrophy is potentially likely [87].

Reducing the periungual soft tissues
Howard–Dubois procedure
This procedure is essential in the treatment of distal embedding. It is also a good approach when dealing with moderate hypertrophic lateral folds. It consists in removing a crescent of soft tissue with a fish-mouth incision carried out parallel to the distal groove around the tip of the toe, about 5 mm below the level of the distal lateral grooves, reaching about 3–5 mm at its maximum width at the distal tip of the phalanx. All incisions are carried down to the bone. Removal of enough soft tissue and suturing the defect resulted in a pulling down of the soft tissue with decompression of the nail [142–144] (Fig. 22.44). Pulling down too much on the distal and lateral walls may induce wound margin necrosis. This procedure is painful and good pain control is mandatory. Some authors have proposed variants of the original technique: removal of a crescent of flesh in the lateral nail fold associated with partial nail avulsion [145] or excision of a triangular piece of the lateral aspect of the toe, termed “lateral foldplasty” [146].

Vandenbos’ procedure
In 1959, Vandenbos and Bowers [147] proposed a theory whereby the excess skin surrounding the nail was burdened with daily weight-bearing, resulting in the bulging of nail fold soft tissues and subsequent pressure necrosis. Recently, Chapeskie and Kovac brought the Vandenbos procedure back into vogue but with some slight modifications. The original procedure involved wide excision of excessive nail fold granulation tissue with preservation of the nail plate and its matrix. The debulking was generous, often leaving a skin and soft tissue defect measuring 1.5–3 mm and occasionally exposing a portion of the distal phalanx (Fig. 22.45). Application of silver nitrate or electrocautery was used to reduce postoperative bleeding. Care was taken at all times not to damage the nail matrix. The wound was then allowed to close via second-ary intention within 4–6 weeks. A total of 124 patients
(164 toes) were treated with the technique for a total of 212 surgical sites with a median follow-up time of 8 years. No recurrences were identified in any patients (100% cure rate), and all cases had excellent cosmetic outcomes [148]. This procedure is very easy to perform, generates very little pain, and has almost no risk of dystrophy. It is recommended in very severe hypertrophy of the lateral nail folds covering a large surface of the nail plate. The main drawback is the long healing time, up to 10 weeks.

**Super U**

This procedure, developed by the Brazilian dermatologist Peres Rosa [149, 150], is very similar to that of Vandenbos. It removes all the excess tissue very generously in a U-shaped manner. The only difference is that it does not include the PNF and that hemostasis is obtained not by electrocautery but by a running lock suture around the wound. Healing occurs by secondary intention without any plate dystrophy (Fig. 22.46).

**Noël’s procedure**

This procedure may be considered as a vertical variant of that of Howard–Dubois. A wedge-shaped ellipse of soft tissue, including the fibrotic and granulation tissue, is removed on both sides of the nail. The incision lines are adjacent to the lateral borders of the nail plate and deep enough (down to the lower third of the lateral aspect of the toe) to remove a large amount of soft tissue. At no time is either the plate or matrix touched. The defect is closed by simple interrupted sutures (Fig. 22.47). Moderate pain
should be foreseen. In a series of 23 patients, complete cure was achieved in all patients with no recurrence after 1 year. Cosmetic outcome was excellent in all cases [151]. This procedure requires more experience than the Howard–Dubois procedure and may be performed if needed only on one side of the toe. The toughest part of the procedure is the skimming curve incision around the bony phalanx. It gives excellent, fast results for hypertrophic lateral walls.

**Tweedie and Ranger’s transposition flap**

This procedure consists of making a transposition flap of the nail wall after preliminary curettage of the granulation tissue in the nail groove (Fig. 22.48). The treatment is effective (over 90% success rate) and not technically difficult [152]. Pain may occur from the transposition. A variant of this procedure was described by Bose, by cutting away the proximal end of the flap and letting the defect heal by secondary intention [153].

**Terminal Syme operation**

The terminal Syme operation is in fact an amputation of the tip of the toe [154]. It involves resection of the nail bed and matrix, amputation of the distal half of the terminal phalangeal bone, and defect closure with a flap formed by the ridged skin of the tip of the toe. It results in a shortened, bulbous toe. As even this method is not free from recurrences, it is a mutilating and obsolete technique.

**Pincer nail**

From adulthood onwards, many people develop a progressive transverse overcurvature that pinches the nail bed and heaps up its distal part. The curvature commonly increases from proximal to distal, giving it a trumpet-like appearance (Fig. 22.49). The condition is quite frequent on toes, but rare on fingers. Other names for this condition include incurved nail, unguis constringens, transverse overcurvature, trumpet nail, convoluted nail, and omega nail. There are several different variants of pincer nails, both hereditary and acquired [155]. The hereditary pincer nail is almost always symmetrical. This form is probably a complex dominant genetic trait with the phalangeal bones being at fault for the development of the overcurvature [156]. Similar nail changes may be seen in other family members. The great toes are usually affected but the smaller toes may also be involved. The great toe commonly shows a lateral deviation of the long axis of the distal phalanx, but the overcurved nails are deviated even more laterally. When the lesser toes are involved they exhibit a medial deviation. This anomaly is seen as early as adolescence and young adulthood. Acquired pincer nails are not symmetrical, though fingernail involvement may be extensive and appear to be fairly symmetrical. Acquired pincer nails may be due to several different causes including dermatoses and drugs (Table 22.2).

Systematic medical imaging has shown that there is always a very wide base of the distal phalanx with osteophytes that are bigger on the medial than on the lateral aspect, explaining why the nail’s longitudinal axis is deviated more laterally than that of the distal phalanx [165]. Usually the whole distal phalanx of the hallux shows a lateral deviation, whereas the involved lesser toes point medially. The nail matrix is intimately attached to the base of the terminal phalanx, and with its widening it becomes uncurved proximally which automatically causes overcurving distally. The heaped-up distal portion
of the nail bed pulls the soft tissue up, resulting in a traction osteophyte [155, 165, 167]. Pain will develop progressively over time, becoming excruciating, impeding the use of footwear, and sometimes making bed sheet contact unbearable. On the other hand it may remain surprisingly painless even though the nail may form a complete tube. Conservative techniques have demonstrated fair results but recurrence is the rule [97]. Two surgical techniques are available: either narrowing of the nail plate – which immediately alleviates pain but often leaves a very narrow nail – or a functional and cosmetic surgical treatment that may be offered to patients with pincer nail associated with dorsal hyperostosis of the distal tuft, known as Haneke’s surgery. Several variants have been described since his original description.

Haneke’s procedure

The aim of this technique is, at the same time, to narrow slightly the nail plate with chemical cautery, remove the bony dorsal distal tuft, and expand the nail laterally, by the use of special reversed tie-over sutures to keep the nail bed stretched over the bone (Fig. 22.50) [165, 167].

The procedure starts with avulsion of two lateral strips of plate and phenolization of the lateral horn of the matrix. This is followed by avulsion of the distal two-thirds of the plate. A median incision of the nail bed from the lunula border to 2 mm beyond the hyponychium is carried down to the bone. During this incision, the traction osteophyte is felt with the scalpel even if it was not obvious on the radiograph. The pinched nail bed is then dissected from the terminal phalanx, as a wide undermining of the bed with the blade skimming the periosseum. The distal dorsal tuft with the osteophyte is rongeured off, and the nail bed is expanded laterally and reapproximated with absorbable 5/0 or 6/0 sutures. Reverse tie-over sutures are placed in the lateral nail folds to keep the nail bed stretched over the bone and are removed after about 3 weeks. In more than 50 patients, a success rate of more than 80% was achieved with this technique.

Suzuki’s variant

This technique is almost identical to that of Haneke. The differences from Haneke’s technique are that: (i) there is no bilateral nail matrix cautery; (ii) the nail plate is completely avulsed; (iii) the lateral nail folds and distal nail fold are cut away; and (iv) the two nail bed flaps are transposed and sutured laterally on the border of the wound resulting from the removal of the lateral and distal nail folds. The resultant triangular defect is covered by a free skin graft. An onycholytic area will develop at the site of the graft [168].

Fanti’s variant

This is considered a variation of Suzuki’s technique [169]. The differences are that: (i) there is bilateral nail matrix cautery; and (ii) the resultant triangular defect is left to heal by secondary intention. This is faster than a graft and resultant onycholysis is less likely.

Kosaka’s variant

This procedure is a bit more demanding and requires a skilled surgeon. The difference from the previous techniques is that the nail bed is elevated as a single W flap and then spread laterally [170].

Zook’s procedure

The aim of the procedure is to flatten the pinched nail bed by elevating the lateral nail bed with dermal grafts, thus preserving the nail matrix and the width of
the nail plate (Fig. 22.51) [171]. After complete avulsion, the paronychial folds are gently freed from the bony attachments bilaterally, using a dental spatula or fine scissors, to elevate the deformed paronychium on both sides, creating two tunnels between the nail bed and the underlying phalanx. The graft is pulled into the tunnel, elevating the paronychial fold. Comparison between autograft and homograft dermis showed that there were no significant differences in the appearance of the nail or relief of symptoms. However, surgical time was much less when homograft dermis was used [172]. Both techniques are considered as a good option for the treat-
ment of transverse overcurvature of the nail [172, 173], but the use of homograft dermis is not allowed in some countries.

Retronychia

This term, which defines a proximal ingrowing nail, was coined by de Berker and Rendall in 1999 (retro means backward, and onychia, nail) [174]. Trauma to the distal nail may induce a transient decrease in nail growth, responsible for the so-called Beau’s line. If nail growth is interrupted for a longer time, onychomadesis occurs: there is no more continuity in the nail plate and a new nail plate slides under the old one and pushes it away progressively until there is nail loss. In retronychia, the old plate adheres firmly to the distal bed and does not migrate further. Successive nail plates pile up under the proximal portion of the previous ones (Fig. 22.52a). This provokes a thickening and an irritation of the nail pocket.

Figure 22.51  Zook’s procedure. (a) Pincer nail on one side of a thumbnail. (b) Distal view of the same patient. (c) The perionychial fold had been freed from its attachment to the periosteum and a dermal graft placed to maintain separation and elevation of the paronychial fold. (d) With both sides involved, the graft is placed bilaterally. (e) The patient 1 year post dermal graft. (f) Distal view at 1 year. © E. Zook.
Nail Surgery

that appears as a subacute paronychia (Fig. 22.52b,c) sometimes with oozing (Fig. 22.52c) or even granulation tissue emerging from under the proximal fold (Fig. 22.52d,e). This is almost always misdiagnosed as an infection. The exudate is responsible for a yellowish hue of the plate [175, 176]. Thus, retronychia may be considered as an onychomadesis that does not evolve in a normal way. Reported cases came from Europe and North Africa, affecting mainly adults, especially women. Children and teenagers are not spared, as reported by Piraccini et al. [177]. Great toenails are most often involved, but fingers may be affected too. Retronychia manifests typically as a triad: arrested nail growth (acknowledged by the patient); subacute paronychia, with the proximal part of the plate being elevated to that of the level of the free edge; and xanthonychia in almost all cases. Some other clinical signs will confirm the diagnosis: granulation tissue sliding out from the undersurface of the PNF, onycholysis, and shortening of the nail bed from the proximal lifting of the nail plate. This gives rise to a bulbous extremity. The condition generates various degrees of pain [175]. The diagnosis is clinical. In very early or doubtful cases, high-resolution ultrasound is of great help (see Chapter 5) [178, 179]. Some minor forms may evolve favorably spontaneously. Early forms should be treated with potent corticosteroids, under occlusive dressings, on the PNF. In cases where this fails and in advanced cases, surgical avulsion is the gold standard. Due to the excessive adherence of the plate to the distal nail bed, proximal avulsion is recommended. It unveils several nail plates piled up. In the vast majority of patients a normal nail will regrow but a permanent dystrophy (thickened and shortened nail) may occur [177]. Recurrence is possible.

Non-scalpel techniques

Radiosurgery

With radiosurgery, the heat is generated in the tissue itself and the main difference from electrocautery is that the electrode remains cold during the procedure. This allows selective matrix destruction with only a very narrow margin of thermal tissue damage. The electrodes are bendable and coated on their upper part, thus avoiding any injury...
to the ventral aspect of the PNF (Fig. 22.53). Destruction of the lateral horn of the matrix is thus possible without injuring the ventral aspect of the PNF using the uncoated side down on the matrix [180]. After avulsion of a lateral strip of nail plate, exposing the lateral horn of the matrix, with the device on “partially rectified current,” the electrode is applied for a period of 3 s to the matrix area, then the power is shut off, the electrode removed, and one waits for 10 s. This procedure is repeated twice when treating a great toe. A drop of corticosteroid cream is instilled into the wound and a sterile compressive dressing is applied [181]. Complete matricectomy is also possible using the same technique after total nail avulsion.

Results are said to be as good as phenolization but no large studies are available [141].

Radiosurgery can be used to treat warts. When the wart is subungual, radiocoagulation is done superficially after partial nail avulsion, followed by a careful curettage of the area because of the fragile nature of the tissue in the nail bed. Hemostasis is obtained with pressure with gauze or aluminum chloride. Pyogenic granulomas can be excised with a cutting loop electrode, providing a specimen for the histologist whilst coagulating the base.

**Cryosurgery in the nail region**

The fingertips and nail apparatus are well endowed with sensory nerve endings. Therefore, unless adequate pre-treatment analgesia is given, cryosurgery to this area may be very painful and resisted by the patient; certainly, without such care, repeat treatments for conditions such as warts may be impossible. It should be pointed out that after the initial freeze and thaw, with all but the shortest freeze times, despite the prominent “burn appearance,” pain is considerably less than with other methods that cause inflammation, unless the periosteum is frozen. Short freeze times may only induce erythema and blister formation, which may be hemorrhagic. Freezing does not damage connective tissue in normal therapeutic doses [182]. For this reason, it has been suggested that it might be tried first before surgery for periungual tumors, especially myxoid pseudocysts [183] type A (over the joint, not in the proximal fold). Some clinicians have used it for Bowen disease (Fig. 22.54). Cryosurgery has long been used by dermatologists for periungual warts.
Nail Surgery

because as with spontaneous healing, when correctly used, scarring should not occur after freezing. However, it is a blind method that does not permit histopathological confirmation of the diagnosis and complete treatment. Freezing of the proximal fold may injure the underlying matrix with resulting transient leukonychia (Fig. 22.55) or permanent nail dystrophy (Fig. 22.56).

Recently, a Turkish team used cryotherapy for ingrowing nails. After local anesthesia and partial reflection of the lateral fold, the lateral matrix horn was frozen for 45 s with open spray and spot-freezing technique using liquid nitrogen. Wound recovery was associated with severe swelling and oozing. There was no evaluation of postoperative pain. Healing was complete at 3 weeks. The authors reported a 97% success rate at 1.5 year follow-up [184].

Trauma

The more adequately an acute injury of the nail is treated initially, the fewer reconstructive procedures will be necessary. Unfortunately, emergency wards disregard the nail unit and only focus on the integrity of the distal digit. This is why, unless a special hand unit surgical team is immediately available, patients seeking medical advice for posttraumatic nail dystrophies always present too late.

Acute injuries

Zook et al. [185] divided nail injuries into simple lacerations, stellate lacerations, severe crush injuries, and avulsions. Closing a finger in a door is the most common source of digit tip injury, followed by smashing between objects, and lacerations from saws and lawn mowers. The age groups most commonly suffering nail injuries are children and young adults (age 4–30 years). The middle finger is the most frequently injured followed in order by the ring, index, little, and thumb. A simple laceration is the most common injury (36%), followed by stellate laceration (27%), crush (22%), and avulsion (15%) in decreasing frequency. Fifty percent of injuries of the nail have an associated fracture of the distal phalanx and/or tuft [185, 186].

Perionychial injury from a sharp object compresses the nail bed between the nail and the bone, resulting in a crushing split of the matrix and bed (Fig. 22.57). When a larger object compresses the nail bed between the nail and the bone, a stellate or multiple fragment type injury results (Fig. 22.58).

Subungual hematoma

A subungual hematoma is an accumulation of blood between two non-expandable rigid structures (bone and plate) that may be responsible for throbbing pain. The thumb and index fingernails are most commonly involved [187]. Surgery should be performed as soon as possible (within 48 h) to alleviate pain and to avoid any dystrophy secondary to a nail bed or matrix laceration. If the hematoma involves less than 25% of the surface of the nail, no drainage is required as pain is limited and blood will be included in the nail keratin (Fig. 22.59) and eliminated with nail growth even before reaching the free edge. If the hematoma covers more than 25% of the surface of the nail it should be drained to relieve pain and to avoid secondary infection (especially fungal) or epithelialization of the bed that may result in permanent onycholysis [187].
Hematoma involving more than 50% of the nail surface should not be surgically explored to rule out any occult laceration of the bed or matrix [188]. This is now considered to be overzealous, as recent large studies have shown that drainage of the hematoma, regardless of its size and its association or otherwise with underlying bone fracture, always cured patients without nail dystrophy [189] even in the fragile nail apparatus of children [190, 191]. Trephination was equal or superior to removal of the nail and formal nail bed repair with significantly lower cost [192]. No complication of drainage was reported in any of the series [190–192].

In any heavy injury, radiography is essential to confirm or rule out a fracture (Fig. 22.60a,b). Perforation of the plate with a heated instrument (red hot paper clip or 18G needle, electrocautery) is easy to perform but the size of the hole is often too small and will be obliterated by the blood clot impairing further drainage. A 2mm punch should be favored as the size of the hole is sufficiently wide [193]. The punch is pushed through the nail plate in the middle of the bloody patch, always ahead of

Figure 22.57 (a) A sharp object striking the nail compresses the nail bed between the nail and the bone, causing a crushing laceration. (b) This type of blow may or may not break the nail but causes localized injury to the nail bed. © E. Zook.

Figure 22.58 (a) A wider dispersed force compresses the nail bed between the nail and the bone, causing a fragmentation injury. (b) With this type of injury the nail bed is frequently exploded into many small pieces. © E. Zook.

Figure 22.59 Small proximal hematoma from a trauma 4 weeks before. The hematoma is being incorporated in the nail plate.
the lunula to avoid injuring the matrix (Fig. 22.61a–d). The procedure should be performed within 48 h after trauma, as the blood is still liquid and can be evacuated very easily by gentle pressure. The nail plate is then pressed onto the bed with a compressive dressing such as adhesive bands or Steri-Strips™ (avoiding covering the hole in the plate) for at least 2 weeks to enhance adherence and avoid any recurrence. Painkillers are usually not necessary as pain is alleviated by drainage.

**Lacerating wounds**

**Simple laceration**

This is the most common injury (36%) to the nail bed (Fig. 22.62). The nail is gently removed using a nail elevator from distal to proximal. The extremity of the elevator is directed toward the nail to avoid further injury to the nail bed and matrix. The avulsed nail is cleaned of dirt and other extraneous material by scraping its undersurface and sides with a scalpel blade or a curette. Dry blood and remnants are removed by wiping it with a gauze pad moistened in 3% hydrogen peroxide. It is then kept in povidone-iodine solution. The nail bed is meticulously repaired. Irregularities are only trimmed if of major extent in order not to sacrifice too much of the unique matrix and nail bed tissue. If necessary, the wound edges are approximated with 7/0 chromic sutures or held in place with acrylic tissue glue [194]. The nail plate is replaced if possible; otherwise a silicone sheet or a plastic nail (Fig. 22.63) or a custom-made nail substitute created from the body of a 10 or 20 mL plastic syringe may be used [195–197]. This nail substitute will not only protect the wound but also mold the irregularities as closely together as possible. A hole is drilled into either the nail or its substitute to allow drainage of any secretion from the wound in an area not directly over the laceration. The nail is held in place under the PNF with sutures through the hyponychium and nail (Fig. 22.64). If the nail was torn out of the nail pocket, the matrix or parts of it may adhere...
to the nail plate. It is then gently separated from the nail and laid back into the proximal groove where it is secured with horizontal mattress sutures that run through the PNF on each side and in the middle (Fig. 22.65). In addition, the matrix is sutured to coapt its margins accurately and to prevent step formation, which in turn would lead to a posttraumatic double nail. Any laceration involving the dorsal surface and the undersurface of the PNF should be repaired with fine sutures of both the ventral

Figure 22.62 (a) Thirty-six percent of nail bed injuries are categorized as simple lacerations. (b) Accurate approximation of the nail bed with fine absorbable sutures is necessary. (c) One year later, a normal nail. © E. Zook.

Figure 22.63 Custom-made nail substitute.

Figure 22.64 A nail wall suture used to retain a Silastic sheet in the nail fold. © E. Zook.

Figure 22.65 (a) The germinal matrix avulsed from the floor of the nail fold. (b) A mattress suture through the nail wall used to reapproximate the germinal matrix into the nail fold. © E. Zook.
Stellate lacerations
A more diffuse blow to the nail results in greater fragmentation of the nail bed and matrix (Fig. 22.66) [23, 198]. Using a head magnifier lens, the nail plate is gently separated from the matrix and nail bed tissue. Fragments are used as free grafts [23, 185, 188, 189]. Suturing or gluing [199] the fragments is necessary. The nail, if not too greatly damaged, is replaced, or a nail substitute is used [197, 200]. Artificial skin is another alternative. For larger defects, a reversed dermal graft is ideal [201].

Crush wounds
These are usually beyond the scope of the dermatological surgeon and taken care of in special trauma units. Again, all nail bed and matrix fragments are collected and returned as accurately as possible (Figs 22.67, 22.68) [185]. A radiograph is essential to rule out a fracture, which must be splinted: if the fracture is stable, the nail plate is returned and usually holds the bone fragments in good position. Unstable fractures and displaced fragments require fixation.

Foreign bodies
Due to its distal position and its role in gripping, the nail with the subungual tissues is naturally exposed to penetration of foreign bodies. Their origin can be plants (thorns, splinter) (Fig. 22.69a–c), animals (sea urchin, oyster shell) (Fig. 22.70a–c), metal, plastic, or glass, this list being non-exhaustive.

Patient seen early
Usually the foreign body cannot be seen. Pain, intense when the accident occurred, is moderate, but touching the nail increases the pain. The foreign body must be removed immediately under local anesthesia with total or partial avulsion of the nail plate. A wet antiseptic dressing must be applied for 2 or 3 days.

Patient seen later on
Subungual infection is the usual reason for the consultation. Diagnosis is easy because of the yellow color of the nail bed and the pulsating pain, especially during the night. Removal of the nail plate over the pus and wide drainage of the cavity should be performed if windowing of the nail is not sufficient [202]. Usually, antibiotics are not needed and an antiseptic dressing can be applied.

Figure 22.66  (a) Twenty-seven percent of nail bed injuries are categorized as stellate lacerations. (b) The proximal nail shown avulsed from the nail fold which is an indication for removal of the nail and exploration of the nail bed. (c) An example of a stellate laceration of the nail bed. (d) Following accurate approximation with 7/0 chromic suture. (e) The nail after removal from the nail bed. (f) The nail after it has been cleaned of attached tissue by scraping. (g) A hole has been burned in the nail to allow drainage and the nail replaced. (h) The finger 1 year later. © E. Zook.
Figure 22.67  (a) Twenty-two percent of injuries are classified as severe crushing injuries. (b) After the nail bed is reapproximated as accurately as possible, a piece of 20/1000 silicone sheeting is placed to mold the nail bed and maintain the nail fold open. (c) The patient 1 year later. © E. Zook.

Figure 22.68  (a) Avulsion of the tip skin, nail bed, and plate. (b) The undersurface of the fragment. (c) The nail is trimmed from around the edge of the fragment to allow accurate approximation of the edge. (d) The skin of the tip is sutured. The bed with the nail attached will maintain the size of the nail bed fragment and facilitate accurate approximation. Steri-Strips™ are used to hold the nail in place. (e) One year later. © E. Zook.
on the wound. Pain relief is obtained immediately and followed by complete recovery within a few days.

Two types of injury deserve special mention.

**Thorns** Thorns of variable origin may induce non-specific inflammatory responses, a suppurative dermatitis with eventual expulsion of the foreign material, or a granuloma with central caseation. In a case of a cactus thorn in the nail bed, a mild inflammatory cell infiltrate with some histiocytes and a few giant cells and neutrophils was observed. The foreign body could be identified as a cactus thorn due to its unique structure: on cross-section, it is circular, made up of hexagonal cells with a round central canal and lined by a single layer of flat cells; under polarized light, it is strongly birefringent. Wood splinters are also birefringent but do not have the round shape and the surrounding layer of flat cells. They may harbor bacteria, fungi, or even algae.

Often the initial injury involving the nail has not been noticed and the patient is examined later on, during the second or third month. There is an uncomfortable, but not really painful, edema of the whole finger, and its mobility is reduced. This is called “inoculation synovitis.” Surgical treatment is compulsory, consisting of the removal of the foreign body as well as the edematous synovial tissue. The color of the latter is grayish and turbid fluid comes out of it. There is no bacterial infection. Recovery takes a few days. A subungual thorn may mimic longitudinal melanonychia.

**Sea urchin granuloma** This condition resembles a whitlow (Fig. 22.70c). A case reports a 35-year-old man with sea urchin granulomas on his left foot including the PNF and matrix of the fourth toe. The toe was swollen, reddish-blue, and tender. The granuloma of the PNF and matrix had caused a broad split in the nail. Histopathology showed a thickening of the proximal fold with loss of the cuticle. There was granulomatous inflammation with lymphocytes, histiocytes, and large foreign body-type giant cells, some of which had large vacuoles. Remnants of the sea urchin spicules could not be discerned [203], but if present they are also
birefringent. Intralesional long-acting corticosteroids are helpful and recovery is seen within 2–3 weeks.

**Burns (thermic and chemical)** (Fig. 22.71)
The nail involvement relates to the severity of the burn, and the final result depends on this and other factors such as the site and depth of the dermal structures involved, the presence of infection, the possibility of keloid formation, and the promptness of treatment.

The signs produced will vary with the degree of the burn: with slight thermal injury, the nail plate turns a brownish-yellow hue [204]; nail bed involvement may result in transient or permanent onycholysis; and a burn of the matrix will lead to loss of the nail, which will be

![Figure 22.71 Burns. (a) Brownish-yellow discoloration. (b) Nail bed involvement with onycholysis (may be permanent). (c) Scarring with nail and joint dystrophy. (d) Black nail due to Hiroshima bomb blast. Courtesy of Mr Takahashi, President of the Hiroshima Peace Memorial Museum. (e) Acute inflammatory changes which lead to severe nail apparatus scarring. Courtesy of A. Tosti.](image-url)
replaced by a dystrophic brownish nail. The extent of the dystrophy reflects the degree of matrix destruction. Involvement of the PNF with subsequent synechiae are among the most severe sequelae and are very difficult to correct. However, Barford’s technique [205] or better procedures derived from this technique [206] may give acceptable results. On the other hand, early excision grafting in severe cases of burning will produce better results.

The damage produced by chemical burns is dependent on the concentration of the irritant and its duration of action. Unlike thermal or electric burns, the destruction will continue after the source of the irritant is removed as long as there is residual, active chemical at the site.

In most cases the burn should be irrigated immediately with copious amounts of water. Solid particles, such as lime, bleaching powder, cement, or phosphorus should be removed first, preferably with a brush, as water may cause the particles to adhere.

Alkali burns are commonly caused by sodium or potassium hydroxide (lyes) or calcium oxide (lime). These agents are found in many drain cleaners and paint removers. The affected site should be irrigated with water for at least 15 min and the alkali then neutralized with vinegar as emergency remedies in the home [207]. Acids produce varying and often characteristic skin discoloration. Hydrofluoric acid burns (Fig. 22.72) should be treated by immersion in lukewarm water until all the surface acid is removed. After irrigation, the burn should be covered with an ointment consisting of one part magnesium oxide and two parts glycerin, which precipitates the fluorine as magnesium fluoride. Hydrofluoric acid may continue to penetrate beneath the surface until it is neutralized by bone; many authorities recommend that the inflamed tissue should be infiltrated with 10% solution of calcium gluconate. In fact, specific treatment consists of intraarterial infusion of calcium gluconate [208].

After the burn has been cleaned and dried, it should be covered with fine mesh gauze soaked in saline. Bulky, dry, sterile dressings are laid over this and held in place by an elastic dressing. The burn area should be elevated to prevent edema, which hinders healing.

Burns are particularly vulnerable to *Clostridium tetani*. Even in the case of minor burns, the patient’s immune status should be checked and the appropriate tetanus prophylaxis instituted.

**Delayed posttraumatic deformities**

**Traumatic malalignment**

Following trauma, scarring in the eponychial area may cause angulation of the nail (Fig. 22.73). The nail bed and matrix are elevated from the periosteum and rotated into normal position. This may require resection of the distal paronychium on the side opposite the angled direction and a graft or flap placed in the defect created when the nail is straightened. When angulation occurs there is significant scarring and although the nail is improved by operation there is usually residual deformity. Development of malalignment of the nail may follow lateral longitudinal biopsy of the nail unit if it was wider than the routine 3 mm diagnostic biopsy. The mechanism of deviation of the distal nail toward the side of excision is still not entirely clear [59] (Fig. 22.74), but may have to do with the proliferation kinetics of the lateral matrix being faster than that of the median part.

**Split nail**

A split nail may be caused by ridging of underlying matrix or by a longitudinal scar in the matrix. Since scar tissue...
does not produce nail cells, the nail becomes thinner and weaker as it grows distally and is prone to crack and break. If the scar is wide, the nail will grow on either side but not in the center, causing a wider split. A longitudinal scar in the nail bed may cause a narrow area of onycholysis.

If the scar causing the split involves the nail bed only, it may be treated by resection of a narrow scar and closure of the defect. If the scar is wide enough to cause a split nail, it is frequently too wide to close successfully without undue wound tension [209] or it requires relaxing incisions on both sides of the nail bed. We have had reasonable success breaking up longitudinal scars by performing one or two Z-plasties in the nail bed, making each limb approximately 2 mm long (Fig. 22.75). A split caused by extensive scarring in the nail bed is best treated by scar resection and split-thickness bed graft from an adjacent area of that finger or a toe [210] (Fig. 22.76). When the split is caused by scar in the matrix, no nail is produced in the germinal matrix and the split is complete. Exploration is essential and requires radial incisions from the corners to expose the matrix. The nail fragments are removed and the nail matrix explored with magnification. Johnson [211] has advocated incisions in the paronychial fold with advancement of the germinal matrix toward the center and suturing. We have had little success with this technique and do not use it for reconstruction following trauma. Our preference is to transplant germinal matrix from a toenail matrix (Fig. 22.77). This graft is harvested somewhat larger than, and shaped to fit, the defect. Matrix grafts will often require ablation of the toe matrix and nail if the second through fifth are used. If more nail matrix is needed, a portion of the great toenail matrix is used. In that case one side is usually used so a portion of the nail can be left. Split-thickness grafts of germinal matrix do not always produce nail and some authors never use them. In our experience, the thickness of the free matrix graft is critical as sufficient subepithelial connective tissue with CD10-positive fibroblasts has to be present for nail production.

A transverse angled scar in the matrix can cause a horizontal double nail. If the ventral portion is adequate, the superficial matrix is excised leaving only the ventral nail (Fig. 22.78). If neither is of adequate volume, the intervening scar must be removed and the wound edges sutured without step formation to make the nail one again.

**Onycholysis**

If onycholysis is distal and unexplained by trauma, removal of the nail and scraping off of the keratinous build-up on the nail bed will often allow the nail to grow normally (Fig. 22.79). The area should be kept as dry as possible during regrowth. If scraping does not correct the non-adherence, a portion of the abnormal nail bed may be replaced with a split-thickness nail bed graft (Fig. 22.80). If the onycholysis is due to scarring, the scar is excised and the defect of the scar covered with a split-thickness nail bed graft from either the adjoining nail or toenail bed (Fig. 22.81). Again, usually if the adjacent nail is not large enough to supply a split-thickness graft, toes (second through fifth) will not be either and the great toe must be used. Dominguez-Cherit and Daniel used hard palate grafts to successfully treat onycholysis [212].

**Hooked nail**

Hooked nail occurs with amputation of the fingertip and loss of bony support of the distal nail bed (Fig. 22.82). Pulling the nail bed and hyponychium over the bone end also causes hooking. Since nail follows the course of the nail bed, the nail hooks distally and volarly. Amputation involving the skin of the tip of the finger has become increasingly treated by secondary healing.
Figure 22.76  (a) Deformity of the nail following nail bed biopsy in the area of the blue marks. (b) The residual of the 3 mm punch biopsy. (c) After the nail plate is removed, an area of scarring is seen at the junction of the nail bed and matrix. (d) The scarred area is resected and a split-thickness sterile matrix graft taken from distally. (e) The split-thickness graft is placed over the defect. (f) The patient's nail 1 year later. © E. Zook.

Figure 22.77  (a) A wide split of the nail with no nail growing in the center portion. (b) A distal view showing the two fragments of nail. (c) A matrix and nail bed graft from the toe gives regrowth of the nail and is shown 1 year later. © E. Zook.

Figure 22.78  (a) A horizontal laceration of the germinal matrix separating the germinal matrix into two portions produces two nails. If the deeper of the two nails is adequate, the superficial remnant is resected, as in this case. If the inferior nail is not adequate then the scar must be removed from between the two fragments of germinal matrix and reapproximated. (b) The patient's nail 1 year later after removal of the superficial germinal fragment. © E. Zook.
Figure 22.79 (a) Chronic detachment of the nail from the nail bed of unknown etiology, but not secondary to trauma. (b) The area of non-adherence is dotted and the area to be removed is outlined. (c) The nail is removed, revealing the hyperkeratinous area of non-adherence. This area is scraped down to normal nail bed. (d) The nail 1 year later. © E. Zook.

Figure 22.80 (a) Extensive non-adherence of the nail to the nail bed of unknown etiology. (b) The nail is removed and a segment of split-thickness nail bed graft from the toe is placed distal to the matrix. (c) The patient 1 year later with much-improved adherence. © E. Zook.

Figure 22.81 (a) Several years post car door crush to the thumbnail with intermittent tearing off of the nail. (b) After the nail fragments are removed, the scar can be seen in the nail bed. (c) A split-thickness nail bed graft from the great toe is harvested and sutured into the scarred area that has been resected. A 20/1000 reinforced sheet of silicone is being placed into the nail fold and over the nail bed. (d) One year post surgery, a near normal nail. © E. Zook.
This gives a good result for fingertip sensation and coverage, but causes some hooking of the nail in most patients. Artificial skin has also successfully been used [201]. The symptomatic (painful) hooked nail may be treated by recreating the defect and allowing the nail bed to return to the dorsum of the distal phalanx. Following this, flap coverage relieves the tension on the nail and usually improves the discomfort but does not correct the cosmetic deformity [213]. To correct a hooked nail completely requires replacement of the distal phalanx, fat, skin, and nail bed. This can only be done dependably by microvascular replacement of the tissue by transferring from a toe tip [214]. Bone grafts onto the distal phalanx with flap coverage as a rule resorb over time and the defect recurs. A prosthesis rather than reconstruction can give a good cosmetic result (see “Nail prosthesis”).

Ridged nail
Nail ridges are caused by scarring of the matrix or nail bed, irregularity of a healed fracture, or non-union of the bony tuft. The nail acquires the shape of the matrix and nail bed, so if the matrix is ridged, the nail will be ridged (Fig. 22.83). Correction of the ridged nail requires surgical removal of the scar or irregular surface of the distal phalanx that is misshaping the nail bed and causing the ridge [215]. Minor transverse ridges of the nail may be seen following ischemic periods of the finger or the body such as extended length of tourniquet time, hypoxia from pneumonia, etc. These resolve as the nail grows.

Ptérygium and eponychial deformities
A ptérygium of the eponychium (dorsal ptérygium) or hyponychium (ventral ptérygium) may occur secondary to trauma, congenital absence, or lichen planus and collagen vascular diseases such as systemic lupus erythematosus and dermatomyositis [216].

Ventral ptérygium may follow injuries that denervate the fingertip or are secondary to ischemia. The pad becomes atrophic and the hyponychium is exposed to minor tip traumas. This is painful and makes the finger extremely tender. The hyponychium is detached from the nail by excising the distal 4–5 mm of the nail bed (including the hyponychium) and replacing it with a split-thickness skin graft. This releases the inverse ptérygia and allows the nail bed to retract under the protection of the nail (Fig. 22.84).

Dorsal ptérygium of the PNF is treated by freeing the dorsal roof of the nail fold from the nail and inserting a silicone sheet beneath it to prevent readhesion until the area has healed (Fig. 22.85). The undersurface of the dorsal roof of the nail fold heals, releasing the adherence. If that is unsuccessful, the dorsal roof may be freed from the nail and a split-thickness nail bed graft placed on the roof of the nail fold to prevent adherence and give improvement in the roughness of the nail (Fig. 22.86) [217]. This technique gives good results.

A notch in the PNF may result from trauma or resection of lesions. Baran [218] has described resection of the lateral edges of the eponychium to create a smooth arc (Fig. 22.87). A notch in the eponychium may be treated with excision and closure, which is not routinely successful because it is closed with tension and will frequently pull apart. Several ways to reconstruct the eponychium have been advocated, including use of transposition and
Figure 22.84  (a) Pterygium of the hyponychium following denervation of the hand and reinnervation which has become painful. (b) The hyponychial area has been excised and a split-thickness skin graft placed in the defect to allow the nail bed to detach from the nail. (c) One year later, the patient's pain has been relieved. © E. Zook.

Figure 22.85  (a) Pterygium of the eponychium causing deformity of the nail. (b) End-on view of the nail deformity. (c) Exploration of the nail fold reveals the scar in the proximal portion of the nail fold where the avulsed matrix had not been replaced. The matrix is elevated from the periosteum and is approximated accurately with horizontal mattress sutures. (d) Anterior view 1 year later with improvement. (e) End-on view showing a smoother nail. © E. Zook.
Nail Surgery

rotation flaps [219], the helical rim of the ear [220] or, our choice, a free composite eponychial graft from a toe. The edges of the defect on the PNF are freshened to allow blood supply and the defect measured (Fig. 22.88). A composite graft of eponychium of a toe (usually the great toe) is used. A fragment of toe eponychium slightly larger than the defect on the finger is removed. The remaining toe eponychium not used is resected and heals secondarily with little deformity. The composite graft is sutured in place and becomes vascularized from the surrounding tissue (Fig. 22.89). Eponychial deformities secondary to burns are very difficult to correct.

Figure 22.86 (a) A nail fold synechia, which causes a split in the nail. (b) End-on view of the deformity of the nail. (c) The nail is removed and the synechia between the dorsal roof and the ventral floor is seen. (d) The synechia is divided. (e) A split-thickness nail bed graft is marked to be removed from the bed. (f) A split-thickness nail bed graft is removed and sutured into the defect in the nail fold. Silastic 21/1000 sheeting is used to maintain the nail fold open. (g) A view of the nail 1 year post repair. (h) End-on view 1 year post repair. © E. Zook.

Figure 22.87 (a,b) Procedure to excise jagged proximal nail tissue to give a better cosmetic result.
A burn of the dorsum of the finger will cause retraction of the eponychium and exposure of the dorsum of the nail with subsequent roughness [221].

Burns of the hand involving the dorsum of the fingers frequently cause nail deformities. The deformity varies from complete absence of the nail to contracture of the dorsal roof with discomfort and roughening of the nail surface. If the nail does not grow, several fingers are usually involved and reconstruction is rarely possible. If deformity is due to retraction of the dorsal roof and does not involve more than a few fingers, eponychial grafts from the toes will frequently improve the appearance and decrease the symptoms. Grafting is carried out as described earlier for eponychial grafts. Achauer and Welk [222] have described reconstruction of the dorsal roof of the nail fold by lateral flaps from the fingertips transposed onto the dorsum of the finger to replace the eponychium. Reconstruction of the eponychium has given improved results through the works of several authors [223–225]. Defects of the PNF from small and medium-sized tumors can be repaired with two transposition flaps for narrow defects and rotation flaps of the nail fold for wider defects [219].

**Absence of nail**

Absence of a nail may be congenital or secondary to trauma, infection, or surgical removal. If toenails are available, they may be transferred as a unit to the finger or, more successfully, may be transferred with microvascular anastomosis [226–231]. If toenails are not available, an area of epidermis the shape and size of the corresponding nail on the opposite hand is excised. A split-thickness or full-thickness skin graft may be applied to the area and, when healed, resembles a nail (Fig. 22.90). One can use a split-thickness skin graft from the nail bed to simulate the body of the nail and a strip of full-thickness skin graft for the lunula and the hyponychium to make these areas white. Creation of a nail fold with a graft has been described into which an artificial nail can be placed [232, 233]. However, in our experience, although satisfactory initially, the fold contracts and after several months there is little or no fold left to accept the proximal edge of the glued-on nail. Composite grafts from the toe to finger to replace a portion (Fig. 22.91) or an entire fingernail (Fig. 22.92) have the loss of a toenail as a consequence.

**Nail prosthesis**

In a wide variety of cases, ranging from deformed nail to complete loss of the terminal phalanx, a silicone rubber, “thimble-shaped” finger cover may be indicated. This prosthesis is easily fitted on the finger stump, encasing
the entire distal phalanx; it must be fine and flexible to maintain pulp sensitivity and must have the same marking and coloring as the finger. The fixation is excellent and the nail form takes nail varnish well [234, 235]. These devices, called Pillet hand prostheses (Fig. 22.93a,b), are available in Paris and several main cities in the USA, Canada, and Italy. When there has been loss of tissue from the distal phalanx, “submini” digital prostheses can also help with that problem [236].

Surgery for congenital abnormalities

Congenital malalignment of the great toenail

The condition and the surgical indications are discussed in Chapter 9. The aim of the procedure is to realign the axis of the nail plate with that of the underlying phalanx. The surgery is performed under general anesthesia for young children. It should be combined with a proximal

Figure 22.90 (a) Amputation of a finger with no nail. The patient wanted to have something that resembled a nail. (b) A split-thickness skin graft in the shape of a nail placed over the distal end of the middle phalanx to simulate a nail. (c) One year later, there has been some fading of the graft but from a few feet away it resembles a nail. © E. Zook.

Figure 22.91 (a) Avulsion of the nail bed and matrix of approximately 40% of the nail. (b) End-on view showing absence of nail growth. (c) The scarred portion of the nail bed is removed. (d) The defect is shown. (e) A fragment of eponychium is harvested from a toe corresponding in size to the defect on the finger. (f) The composite graft with a nail attached is sutured in place into the defect on the finger. (g) Anterior view 1 year later showing nail growth. (h) End-on view of the new nail growth. © E. Zook.
Figure 22.92  (a) A lack of nail growth and angulation secondary to premature closure of the growth plate following trauma. (b) The finger is compared with the toes to find a corresponding sized nail. It is elected to use the second toe although the length of the second toenail is usually not as long as that of the finger. (c) The donor toe is marked. (d) The nail, bed and matrix, and hyponychium are excised as a unit and the composite graft transferred to the finger. (e) The composite graft is sutured into the defect and nail fold. (f) One year postgraft finger. Better adherence distally could be attained if the bed was lengthened with a nail bed graft. (g) A second toe post closure. © E. Zook.

Figure 22.93  (a) Traumatic dystrophy. (b) Toe prosthesis.
digital block with either ropivacaine 1% or bupivacaine 0.5%, which allows the general anesthesia to be very light and guarantees a pain-free period of 12–24 h. For older or cooperative children, surgery may be performed under local anesthesia.

First, an incision is carried around the tip of the toe approximately 5 mm below the level of the nail bed. Another incision is performed at the toe tip such as to yield a crescentic wedge of soft tissue that is slightly wider on the antero-lateral aspect. Then, the whole nail unit is meticulously dissected from the phalanx, which at this age might not yet be fully mature, while remaining directly on the bone. Care should be taken not to perforate the nail bed while dissecting the nail bed and matrix from the underlying bone. The dissection should extend up to the joint without damaging the extensor tendon. In most instances, the distal dorsal tuft of the distal phalanx is hypertrophic, pointing upwards (dorsally). It has to be removed to give a straight surface of the distal phalanx. The entire nail apparatus can be elevated as an unguo-dermal flap and rotated into the correct axis of the toe (Fig. 22.94a–d) [237]. Slight overcorrection is sometimes advisable. Whether or not Burrow’s triangles are taken to facilitate rotation depends on the degree of malalignment. Avoiding removal of Burrow’s triangles may avoid further damage to the arterial blood supply. The unguo-dermal flap is then sutured in its correct position with 4/0 stitches. The results of this unguo-dermal rotation are usually good in little children. The older the patient, however, the less likely is good nail growth after surgery. However, a new, smooth, well-aligned nail may grow out but remain short because of the long-standing onycholysis with epithelialization of the bed.
Trapezoidal nails

Trapezoidal nails are a congenital nail dystrophy where the nail plate appears too wide for its bed. The nail appears to widen distally as its proximal part remains hidden by the proximal portion of the lateral nail folds. This actually results from an imbalance between the proximal and the lateral nail fold: their junction occurs medially, the proximal fold being too narrow. This dystrophy would only be a curiosity if it did not promote the arising of a hypertrophic lip or even distal lateral onychocryptosis in some patients (Fig. 22.95a). The goal of treatment is permanent narrowing of the nail plate, either to achieve cure of ingrown toenail or for cosmetic reasons. The nail should be narrowed to have the junction of the proximal and lateral fold perpendicular (Fig. 22.95b). Chemical cautery is the best choice. This procedure allows the lateral nail folds to flatten. They fill the space previously occupied by the portion of avulsed nail.

Racket nails

This term refers to a congenital malformation of the thumbs resulting in brachyonychia, the width of the nail plate and nail bed being greater than their length. Clinically the thumb exhibits a gross, short, and broad terminal phalanx that usually lacks the lateral nail fold (Fig. 22.96). Racket thumbs are usually inherited as an autosomal dominant trait; females are three times more affected than males. It symmetrically affects the thumbs but some cases may be asymmetrical and involve only one thumb. Exceptionally, all fingernails are affected. This deformity is caused by early obliteration of the epiphyseal line of the thumbs while periosteal growth continues, leading to a wider and shorter bony phalanx covered with a nail plate of a similar shape [238]. For patients who want surgery, narrowing the nail plate and recreating lateral nail folds may improve the esthetic appearance. Two lateral excisions, in the shape of a so-called “lazy S,” are performed on both sides of the thumbnail exactly as performed for a lateral longitudinal biopsy. The lateral soft tissue aspects of the distal phalanx are dissected from the bone almost down to the volar aspect. Back stitches (non-absorbable 3/0 suture) will recreate lateral nail folds. The needle is run into the lateral aspect about 2–3 mm volar to the plane of the nail bed–bone interface, through the nail bed and plate, and back again through the lateral thumb skin, which upon knotting will be elevated, thus forming a lateral nail fold [239]. A second, later procedure might be to lengthen the shape of the plate by removing a crescent of the PNF as performed in chronic paronychia.

Vertical implantation of the fifth toenail

In this rare disorder, the aberrant implantation of the matrix of the fifth toenail is responsible for its vertical growth (Fig. 22.97). In addition to the esthetic inconvenience, it generates real discomfort, especially when pulling on stockings or socks, the nail being pushed backwards. Ladies mostly complain of ruining their stockings. Treatment is total nail ablation, either with chemical cautery or steel blade excision. The latter procedure should provide a careful dissection of the matrix [240].

Complications in nail surgery

Complications may be reduced to a minimum by preventative measures, such as careful patient selection, sterile technique, adequate and accurate procedure, and meticulous care of the nail matrix. Their early recognition and management is part of the patient’s follow-up.
Surgery of the nail is not recommended in high-risk patients, but the importance of systemic disease in nail abnormalities is often overemphasized. A history of concomitant administration of drugs may be relevant. They may affect anesthesia (such as monoamine oxidase inhibitors or phenothiazines), prolong bleeding (such as aspirin or anticoagulants), delay healing (such as corticosteroids), or have toxic effects on the nail. There may be a history of allergy to lidocaine or mepivacaine. Parabens are contained in both as a preservative.

**Pain**

Intraoperative pain may be due to improper anesthesia technique or insufficient time allowed for the anesthetic to work. Pain was reported at some point during Mohs micrographic surgery, especially by patients who spent a long time in surgery. Additional preventative measures could be considered in patients at higher risk [241].

Postoperative pain is discussed under “Postoperative pain management.”

**Dysesthesia**

The occurrence of postoperative long-term dysesthesia after nail surgery is a phenomenon well known to experienced nail surgeons. A sensory disturbance is observed in about half of the patients without any relationship to the extent of the surgery undertaken. The most frequently reported sensations were numbness or loss of sensation and tingling. Locations of altered sensation were in decreasing order (Fig. 22.98): the digit tip (34%), the PNF (28%), and the margin beneath the free edge of the nail (24%). Complete or partial resolution occurred after 6–12 months, however about 10% had no improvement. There is so far no clear explanation for this phenomenon [242].

**Bleeding**

Intraoperatively, check the tourniquet. Postoperative bleeding within the wound may lead to hematoma. After surgery, use 35% aluminum chloride and oxidized cellulose. However, as the vessels involved are small, the bleeding can usually be controlled by direct pressure. For severe bleeding, injection of some anesthetic as a wing block will act as a volumetric tourniquet.

**Infection**

Strict antiseptic technique should be used as the nail unit lies on the phalanx directly below, with little intervening dermis and no subcutaneous tissue. The surgical procedure almost always extends to the periosteum, posing a risk of osteomyelitis should the sterile field be compromised. Most of the time, infection results from poor homecare and/or lack of hygiene (Fig. 22.99). Antibiotic prophylaxis should be prescribed only for prevention of endocarditis and joint prosthesis infection. If infection occurs, sample the pus and prescribe an antistaphylococcal antibiotic.

**Necrosis**

Necrosis is an unpredictable complication. The condition may involve the whole extremity or a very small limited area (Fig. 22.100). Cases of digital necrosis have been described after accidental extended use of a tourniquet [243]. It may also be caused by the use of lidocaine with epinephrine in patients with impaired blood supply of the limbs [31], from overtight stitches, or from excess volume infiltration of local anesthetic.
Spicules

Nail spicules are the main complication after lateral matricectomies, lateral longitudinal excisions, or total nail apparatus removal. Post-phenolization nail spicules are most often seen in the first 3 months after surgery in the proximal nail groove or in the middle of the PNF (Fig. 22.43). Crush injuries leave many small pieces of subungual tissue. If these fragments are not incorporated into the repair, some may grow independently and cause nail horns or spicules.

Temporary abnormalities

After surgery, the nail grows less rapidly and then faster for 50 days. This will result in a bump that will eventually grow off to leave a flat nail. A longitudinal nail fissure may be observed after matrix scarring of 3 mm or more.

Permanent abnormalities

These may lead to unsightly scarring.

- **Dorsal pterygium**: Repositioning the nail plate should avoid this complication. If the width of the dorsal pterygium is small, repair may be attempted. The proximal nail plate fusion is separated from the matrix and the scar is excised and sutured with 6/0 absorbable sutures. The ventral surface of the PNF is grafted with a split-thickness nail bed graft [210]. For operations involving the lunula border, it is cosmetically important to maintain the curvilinear configuration of the distal lunula which plays an important role in shaping the free edge of the nail plate.
- **Onycholyis** can occur after removal of tumors of the phalanx or when the nail bed is widely torn. In severe cases a split-thickness nail bed graft taken from the great toe may be useful.
- **Ventral pterygium**: Hyponychial interventions may leave a painful ventral pterygium. If topical treatment with hydroxychitosan fails, a strip of nail bed and hyponychium is resected and replaced by a split-thickness skin graft.
- **Nail deformities** have occurred from drilling the nail plate to release subungual hematoma and from rough or careless removal of the nail to expose the bed. Nail deformities may also occur from the use of Vicryl® sutures in nail bed repair. These sutures, if too large, dissolve too slowly and are still present during new nail growth. This can produce an area of onycholysis and ridging in the nail.
- **Longitudinal erythronychia or leukonychia** may be secondary and result from any matrix scarring.
- **Longitudinal nail fissure** may be persistent or secondary to longitudinal nail unit excision.
- **Lateral deviation** of the nail plate may result from lateral longitudinal biopsy wider than 3 mm. CO₂ laser treatment for periungual warts can produce the same abnormality.

Recurrence

Recurrences will depend on the nature of the original lesion.

Implantation cyst

An epidermoid inclusion cyst may appear in a postoperative scar. They are a well-known but not a frequent complication of nail surgery. They are associated with suturing and needle trauma and may arise from any type...
of surgery involving the nail apparatus (Fig. 22.101). They were reported as being the most common complication after full-thickness grafts following complete nail unit excision [80].

**Reflex sympathetic dystrophy**

Reflex sympathetic dystrophy, better known as "complex regional pain syndrome" (CRPS) type 1, is exceptional after nail surgery [244, 245]. It presents with pain, sensory and motor disturbances, along with autonomic and even soft tissue trophic changes. Nail changes reported in the setting of CRPS include increase of linear nail growth, nail overcurvature, leukonychia, Beau’s line, trachyonychia, brittleness, paronychia, and clubbing. Toes are usually spared.

CRPS type 1 is mainly distinguished from type 2 by the lack of preceding nerve injury/surgery. CRPS is more common in the upper extremity in women aged between 50 and 60. Toes are usually spared. As there are no specific tests available, diagnosis is made using the Budapest clinical criteria.

**Hypertrophic scar and keloid**

Hypertrophic scar and keloid may involve the PNF or the nail bed (Fig. 22.102). Surprisingly, hypertrophic scars and keloids at the nail unit are not described as more frequent in black people. Intrallesional corticosteroid injections and silicone gel and/or pads are usually effective.

**Postoperative pain management**

Postoperative pain management relies on two points: elevation of the limb and pain killers.

**Elevation of the limb**

Elevation of the limb will ease throbbing and facilitate healing. It will avoid edema at the surgical site that may be responsible for pain and may pull on the sutures. The patient should wear a sling if the surgery involves a finger, and the foot should be elevated using a footstool. If a commercial sling is not available, a large square scarf will do very well. It should be placed by the surgeon or the nurse immediately after the dressing is performed. The duration of elevation of the limb is 2 days, equal to the inflammatory reaction after surgery.

**Pain killers**

The surgeon should accurately determine the degree and duration of pain of the surgery to adapt the postoperative analgesia. Some procedures are less painful than others. For example, phenolization, tangential excision, ligation of the peduncle of a myxoid pseudocyst, and, surprisingly, removal of a subungual exostosis, induce very little pain. Lateral longitudinal biopsy, nail avulsion, excision of the whole nail unit, and small flaps on the bed are painful. The most painful is rotation of the whole nail unit for nail malalignment.

Initial postoperative pain management starts with adequate anesthesia (see “Anesthesia”). Long-lasting anesthetics (up to 15 h) are essential for painful surgery. These (bupivacaine or ropivacaine 5–10 mg) may be injected postoperatively.

Prescription of paracetamol 500 mg every 4 h on the first day then three times on the second day will suffice in most cases. Patients may be instructed to add antiinflammatory agents such as ibuprofen, naproxen, or meloxicam if needed. These agents do not increase the risk of bleeding [245]. For moderate pain, the combination of paracetamol and codeine works well. If severe pain is expected, mild
opioid narcotic analgesics (dextropropoxyphene, tramadol, naloxone combined with tilidine) should be prescribed and precise dosing and side-effects explained.

Dressings

In nail surgery, postoperative dressings must have three main properties: non-adherence, absorbency, and perfect fixation. Adapted footwear is essential.

Non-adherent dressing

Applying large amounts of ointment (possibly containing antiseptics) covered with a non-adherent dressing such as petrolatum-coated gauze (tulle gras, Bactigras, Adaptic, Jelonet) possibly with added antiseptics (Betadine Tulle, Fucidin Tulle) will protect the wound from drying and allow easy and painless removal. Telfa covered dressings are another option. Recently, a new category of dressing that is well adapted to nail surgery appeared on the market. It consists of a porous, semitransparent, low-adherent, flexible polyamide net coated with soft silicone (Mepitel). It is not absorbent but contains apertures of approximately 1 mm in diameter that allow the passage of exudate into a secondary absorbent dressing.

Absorbent dressing

As postoperative bleeding may be noticeable, a bulky dressing made of two or three loose layers of mesh gauze, placed over the non-adherent dressing, will absorb bleeding and provide protection against trauma. Elevation of the limb will limit bleeding.

Securing the dressing

Tubular gauze or net may be used but control of the pressure on the dressing is impossible. A narrow elastic bandage (4 cm) is a more flexible form of dressing as it may apply more precise pressure over the wound. The elastic bandage is applied in a U-shaped fashion in order to avoid any possibility of its acting as a tourniquet. The last layers may be circular and will include wrapping around the wrist or ankle to fully secure the dressing. This should afford light compression that does not compromise blood flow [8].

Dressing removal and replacement

Patients fear pain from sticky dressings that are abruptly pulled off. In most instances, the dressing will not stick to the wound even if there is almost always some bleeding into the dressing. The dressing is removed on the second day post surgery. Sometimes early removal is necessary after 24 h if bleeding is severe, because the impregnated gauze of the bulky dressing dries and becomes stiff and may cause unpleasant or painful compression. If left in place too long, dry and hard dressings may induce superficial erosion on the skin of the proximal and/or lateral nail folds [135]. In case of adherence, soaking in lukewarm water will detach the dressing spontaneously.

Further care will depend on the type of surgery. Usually, the dressing should be renewed twice per day for the first few days. A large commercial plaster will easily cover a great toe or a finger. Greasy antiseptic ointment should be applied for the first 2 weeks to avoid the wound to dry. Then antiseptic solution should be applied twice a day until healing is complete.

References

12 Alam M, Goldberg LH. (2002). Serious adverse vascular events associated with perioperative interruption of


Nail Surgery


110 Vaccari S, Dika E, Balestri R et al. (2010). Partial excision of matrix and phenolic ablation for the


Chapter 22


### Appendix

**Mark Holzberg**

*Department of Dermatology, Emory University School of Medicine, Atlanta, GA, USA*

Differential diagnosis of nail findings (onychopathy) in both color and shape by anatomical site. The references for the associated diseases may be found in the appropriate section in the text.

<table>
<thead>
<tr>
<th>Nail anatomical site</th>
<th>Onychopathy</th>
<th>Associated disease</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Proximal nail fold</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Color</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Bleeding</td>
<td>Neurological</td>
<td>Major peripheral and/or central neurological deficits</td>
</tr>
<tr>
<td>Blue</td>
<td>Dermatological</td>
<td>Blue nevus</td>
</tr>
<tr>
<td></td>
<td>Toxicity</td>
<td>Argyria</td>
</tr>
<tr>
<td>Brown</td>
<td>Hereditary or congenital</td>
<td>Congenital nevus</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Laugier–Hunziker–Baran syndrome</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Peutz–Jeghers syndrome</td>
</tr>
<tr>
<td></td>
<td>Neoplastic</td>
<td>Hutchinson's sign (melanoma)</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Lentigo</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Nevus</td>
</tr>
<tr>
<td></td>
<td>Malnutrition</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Drugs</td>
<td>Argyria</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Amlodipine</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Minocycline</td>
</tr>
<tr>
<td>Red</td>
<td>Infectious</td>
<td></td>
</tr>
<tr>
<td>Bywaters lesions (infarcts)</td>
<td>Gonococemia</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Rheumatological</td>
<td>Dermatomyositis</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Granulomatosis with polyangiitis (Wegener granulomatosis)</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Rheumatoid arthritis</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Systemic sclerosis</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Vasculitis</td>
</tr>
<tr>
<td>Capillary telangiectasias</td>
<td>SLE pattern</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>Sjögren syndrome</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Systemic lupus erythematosus</td>
</tr>
<tr>
<td>Nail anatomical site</td>
<td>Onychopathy</td>
<td>Associated disease</td>
</tr>
<tr>
<td>---------------------</td>
<td>-------------</td>
<td>--------------------</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Scleroderma–dermatomyositis pattern</td>
</tr>
<tr>
<td></td>
<td></td>
<td><em>Borrelia burgdorferi</em> infection</td>
</tr>
<tr>
<td></td>
<td></td>
<td>CREST</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Dermatomyositis</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Mixed connective tissue disease</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Raynaud phenomenon</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Systemic sclerosis</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Non-specific pattern</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Autoimmune</td>
</tr>
<tr>
<td></td>
<td></td>
<td>SAVI Syndrome (STING associated vasculopathy of infancy)</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Cardiovascular</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Aortic insufficiency, associated with Quincke's pulse</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Gastrointestinal</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Crohn's disease</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Cystic fibrosis</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Vascular</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Acrocyanosis</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Angiokeratoma corporis diffusum (Fabry disease)</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Henoch–Schönlein purpura</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Infectious</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Hepatitis C viral infection</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Immunodeficiency</td>
</tr>
<tr>
<td></td>
<td></td>
<td>AIDS</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Rheumatological</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Antisynthetase syndrome</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Behçet disease</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Henoch–Schönlein purpura</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Morphea</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Rheumatoid arthritis</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Occupational</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Coffee exposure (in plantation workers)</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Metabolic</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Homocystinuria</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Drugs</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Atenolol</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Miscellaneous</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Graft-versus-host disease</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Schizophrenia</td>
</tr>
<tr>
<td>Osler's nodes</td>
<td>Cardiovascular</td>
<td>Bacterial endocarditis</td>
</tr>
<tr>
<td>Paronychia</td>
<td>Hereditary or congenital</td>
<td>Acromegaly</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Congenital ingrown toenails</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Dyskeratosis congenita</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Ectodermal dysplasia, hidrotic, Clouston syndrome</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Ichthyosis follicularis with alopecia</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Multiple cartilaginous exostosis</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Diaphyseal aclasis</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Pachyonychia</td>
</tr>
<tr>
<td></td>
<td></td>
<td>congenita type 1 of Jadassohn-Lewandowsky Tricho-oculo-dermal vertebral syndrome (arthrogryposis and ectodermal dysplasia)</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Zinsser–Engman–Cole syndrome</td>
</tr>
<tr>
<td></td>
<td>Renal</td>
<td>Hemodialysis</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Renal transplant patients</td>
</tr>
<tr>
<td>Nail anatomical site</td>
<td>Onychopathy</td>
<td>Associated disease</td>
</tr>
<tr>
<td>----------------------</td>
<td>-------------</td>
<td>--------------------</td>
</tr>
<tr>
<td><strong>Proximal nail fold</strong> (cont'd)</td>
<td>Red (cont'd)</td>
<td>Neurological</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Encephalitis</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Glioma</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Multiple mucosal neuroma syndrome</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Neurofibroma</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Neuropathies</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Reflex sympathetic dystrophy</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Schwannoma</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Syringomyelia</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Systematized multiple fibrillar neuroma</td>
</tr>
<tr>
<td>Endocrine</td>
<td></td>
<td>Cushing syndrome</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Diabetes</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Hypoparathyroidism</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Polyglandular autoimmune syndrome type I</td>
</tr>
<tr>
<td>Vascular</td>
<td></td>
<td>Acrocyanosis</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Digital ischemia</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Raynaud phenomenon and disease</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Thromboangiitis obliterans</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Vasospasm</td>
</tr>
<tr>
<td>Infectious</td>
<td></td>
<td>Bacterial</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Classical</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Erysipeloïd</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Leprosy</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Milker's nodule</td>
</tr>
<tr>
<td></td>
<td></td>
<td><em>Mycobacterium marinum</em></td>
</tr>
<tr>
<td></td>
<td></td>
<td><em>Mycobacterium tuberculosis</em></td>
</tr>
<tr>
<td></td>
<td></td>
<td>Orf</td>
</tr>
<tr>
<td></td>
<td></td>
<td><em>Pseudomonas</em> spp.</td>
</tr>
<tr>
<td></td>
<td></td>
<td><em>Staphylococcus</em> spp.</td>
</tr>
<tr>
<td></td>
<td></td>
<td><em>Streptococcus</em> spp.</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Syphilis</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Tuberculosis</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Tularemia</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Unusual</td>
</tr>
<tr>
<td></td>
<td></td>
<td><em>Actinobacillus actinomycetemcomitans</em></td>
</tr>
<tr>
<td></td>
<td></td>
<td><em>Bartonella henselae</em></td>
</tr>
<tr>
<td></td>
<td></td>
<td><em>Corynebacterium</em> spp.</td>
</tr>
<tr>
<td></td>
<td></td>
<td><em>Eikenella corrodens</em></td>
</tr>
<tr>
<td></td>
<td></td>
<td><em>Klebsiella pneumoniae</em></td>
</tr>
<tr>
<td></td>
<td></td>
<td><em>Serratia marcescens</em></td>
</tr>
<tr>
<td></td>
<td></td>
<td><em>Torulopsis maris</em></td>
</tr>
<tr>
<td>Fungal</td>
<td></td>
<td><em>Aspergillus niger</em></td>
</tr>
<tr>
<td></td>
<td></td>
<td>Blastomycosis</td>
</tr>
<tr>
<td></td>
<td></td>
<td><em>Blastoschizomyces capitatus</em></td>
</tr>
<tr>
<td></td>
<td></td>
<td><em>Candida</em> spp.</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Chromoblastomycosis</td>
</tr>
<tr>
<td></td>
<td></td>
<td><em>Coccidioidomycosis</em></td>
</tr>
<tr>
<td></td>
<td></td>
<td><em>Curvularia lunata</em></td>
</tr>
<tr>
<td></td>
<td></td>
<td><em>Fusarium</em> spp.</td>
</tr>
<tr>
<td></td>
<td></td>
<td><em>Microsporum gypseum</em></td>
</tr>
<tr>
<td></td>
<td></td>
<td>Mycetoma</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Paracoccidioidomycosis</td>
</tr>
<tr>
<td></td>
<td></td>
<td><em>Scopulariopsis brevicaulis</em></td>
</tr>
<tr>
<td></td>
<td></td>
<td><em>Scytalidium</em> spp.</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Sporotrichosis</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Trichosporum beigelii</td>
</tr>
<tr>
<td>Nail anatomical site</td>
<td>Onychopathy</td>
<td>Associated disease</td>
</tr>
<tr>
<td>---------------------</td>
<td>-------------</td>
<td>--------------------</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Parasitic</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Leishmaniasis</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Tungiasis</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Viral</td>
</tr>
<tr>
<td></td>
<td></td>
<td><em>Herpes simplex</em></td>
</tr>
<tr>
<td></td>
<td></td>
<td><em>Herpes zoster</em></td>
</tr>
<tr>
<td></td>
<td></td>
<td>Immunodeficiency</td>
</tr>
<tr>
<td></td>
<td></td>
<td>AIDS</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Chronic mucocutaneous candidiasis</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Deficient interleukin-2 secretion</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Immunodeficiency</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Interleukin-2 deficiency</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Job syndrome</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Multiple carboxylase deficiency</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Wiskott–Aldrich syndrome</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Neoplastic</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Acrokeratosis paraneoplastica of Bazex</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Bizarre parosteal osteochondromatous proliferation of the tubular bones</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Bowen disease</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Chronic lymphocytic leukemia</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Cutaneous T-cell lymphoma</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Enchondroma</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Epithelioid hemangioma</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Glucagonoma</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Histiocytosis X</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Kaposi sarcoma</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Keratoacanthoma</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Malignant melanoma</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Metastasis</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Myxoid cyst</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Osteoid osteoma</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Paraneoplastic pemphigus</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Sarcoma</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Tumor</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Enchondroma</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Exostosis</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Metastasis</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Orthopedic</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Myxoid pseudocyst</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Rheumatological</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Rheumatoid arthritis</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Systemic lupus erythematosus</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Systemic sclerosis</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Dermatological</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Artificial nails</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Atopic dermatitis</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Contact dermatitis, e.g. to acrylates, local anesthetics, foods, hydroxyamine, bryozoan invertebrates (“moss animals”), topical medications, rubber, food hypersensitivity, <em>Candida</em> hypersensitivity</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Darier disease</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Erythema elevatum diutinum</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Erythema multiforme</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Finger sucking</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Frostbite</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Granulomas</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Hidrotic ectodermal dysplasia</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Ingrown toenails</td>
</tr>
<tr>
<td>Nail anatomical site</td>
<td>Onychopathy</td>
<td>Associated disease</td>
</tr>
<tr>
<td>---------------------</td>
<td>-------------</td>
<td>--------------------</td>
</tr>
<tr>
<td><strong>Proximal nail fold</strong> (cont’d)</td>
<td>Red (cont’d)</td>
<td>Keratosis lichenoides chronica</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Leukemia cutis</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Lichen nitidus</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Lichen planus</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Pachyonychia congenita</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Parakeratosis pustulosa</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Pemphigoid</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Pemphigus</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Pernio</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Psoriasis</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Reiter syndrome</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Repeated microtrauma</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Retronychia</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Rubinstein–Taybi syndrome</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Stevens–Johnson syndrome</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Toxic epidermal necrolysis</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Malnutrition</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Acrodermatitis enteropathica</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Zinc deficiency</td>
</tr>
<tr>
<td><strong>Drugs</strong></td>
<td></td>
<td>Acitretin</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Cefalexin</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Chemotherapeutic agents</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Cyclophosphamide/vincristine</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Docetaxel</td>
</tr>
<tr>
<td></td>
<td></td>
<td>5-Fluorouracil</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Methotrexate/leucovorin</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Mercaptopurine</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Cocaine</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Ciclosporin</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Epidermal growth factor receptor inhibitors</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Etretinate</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Everolimus</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Isotretinoin</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Lamivudine</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Phenolphthalein</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Protease inhibitors</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Indinavir</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Lopinavir</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Nelfinavir</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Ritonavir</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Salbutamol</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Sulfonamide antibiotics</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Temsirolimus</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Topical 5-fluorouracil</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Zidovudine</td>
</tr>
<tr>
<td><strong>Toxicity</strong></td>
<td></td>
<td>Radiodermatitis (chronic)</td>
</tr>
<tr>
<td><strong>Trauma</strong></td>
<td></td>
<td>Foreign body injury, e.g. plants or woods</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Frozen packaging in shrimp shelling workers</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Occupational</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Onychophagia</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Piano, harp, or violin playing</td>
</tr>
<tr>
<td><strong>Miscellaneous</strong></td>
<td></td>
<td>Amyloidosis</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Bizarre parosteal osteochondromatous proliferation</td>
</tr>
<tr>
<td></td>
<td></td>
<td>of the tubular bones</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Graft-versus-host disease</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Sarcoidosis</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Yellow nail syndrome</td>
</tr>
<tr>
<td>Nail anatomical site</td>
<td>Onychopathy</td>
<td>Associated disease</td>
</tr>
<tr>
<td>---------------------</td>
<td>-------------</td>
<td>--------------------</td>
</tr>
<tr>
<td><strong>Shape</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Dorsal pterygium</td>
<td>Idiopathic</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Idiopathic atrophy of the nails</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Hereditary or congenital</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Congenital subungual pterygium</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Dyskeratosis congenita</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Marfan syndrome</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Nail–patella syndrome</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Zinsser–Engman–Cole syndrome</td>
<td></td>
</tr>
<tr>
<td>Endocrine</td>
<td>Diabetic vasculopathy</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Inadequate corticosteroid matrix</td>
<td></td>
</tr>
<tr>
<td>Vascular</td>
<td>Atherosclerosis</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Diabetic vasculopathy</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Peripheral ischemia</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Raynaud phenomenon and disease</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Systemic lupus erythematosus</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Vasospasm</td>
<td></td>
</tr>
<tr>
<td>Infectious</td>
<td>Infiltration for Candida paronychia</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Type 2 lepra reaction</td>
<td></td>
</tr>
<tr>
<td>Rheumatological</td>
<td>Systemic lupus erythematosus</td>
<td></td>
</tr>
<tr>
<td>Dermatological</td>
<td>Acrokeratoelastoidosis</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Cicatricial pemphigoid</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Discoid lupus erythematosus</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Lichen planus</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Onychomatricoma</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Onychotillomania</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Pemphigoid</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Pemphigus foliaceus</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Porokeratosis of Mibelli</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Toxic epidermal necrolysis</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Unilateral generalized linear porokeratosis</td>
<td></td>
</tr>
<tr>
<td>Drugs</td>
<td>Etanercept</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Nifedipine</td>
<td></td>
</tr>
<tr>
<td>Toxicity</td>
<td>Burns</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Radiodermatitis</td>
<td></td>
</tr>
<tr>
<td>Trauma</td>
<td>Onychotillomania</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Trauma, isolated or repeated</td>
<td></td>
</tr>
<tr>
<td>Miscellaneous</td>
<td>Graft-versus-host disease</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Sarcoidosis</td>
<td></td>
</tr>
<tr>
<td>Papules/pebbling</td>
<td>Endocrine</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Diabetes</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Infectious</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Human papillomavirus</td>
<td></td>
</tr>
<tr>
<td>Tumor</td>
<td>Smooth</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Acral pseudolymphomatous angiokeratoma of children (APACHE)</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Angiokeratoma circumscriptum</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Amelanotic melanoma</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Basal cell carcinoma</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Chondro- or osteosarcoma</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Coccal nail fold angiomatosis</td>
<td></td>
</tr>
<tr>
<td>Nail anatomical site</td>
<td>Onychopathy</td>
<td>Associated disease</td>
</tr>
<tr>
<td>---------------------</td>
<td>-------------</td>
<td>--------------------</td>
</tr>
</tbody>
</table>
| **Proximal nail fold** (cont’d) | Tumor (cont’d) | Dermatofibrosarcoma  
Dermatomyofibroma  
Eccrine angiomatous hamartoma  
Eccrine poroma  
Epithelioid hemangioendothelioma  
Epithelioid sarcoma  
Erythema elevatum diutinum  
Fibroma  
Fibrosarcoma  
Ganglion  
Giant cell tumor  
Glioma, neurilemmoma, schwannoma  
Granuloma annulare  
Hidradenocarcinoma  
Histiocytoid hemangioma  
Histiocytoma  
Infantile digital fibromatosis  
Juvenile hyaline fibromatosis  
Juvenile xanthogranuloma  
Keloid  
Koenen periungual fibromas  
Lipoma  
Lymphangioma circumscriptum  
Malignant fibrous histiocytoma  
Malignant synovial tumor  
Merkel cell carcinoma  
Metastatic tumor  
Multicentric reticulohistiocytosis  
Myxoid pseudocyst  
Necrobiotic granuloma  
Neurofibroma  
Osteoma cutis  
Oxalate granuloma  
Periungual and subungual arteriovenous tumors  
(cirrhotic angioma)  
Pyogenic granuloma  
Recurring digital fibrous tumors of childhood  
Reticulohistiocytoma  
Rheumatoid nodule  
Tendinous xanthoma  
Verrucous  
Acquired ungual fibrokeratoma  
Actinic keratosis  
Arsenical keratosis  
Bowen disease  
Epithelioma (carcinoma) cuniculatum  
Granular cell tumor  
Incontinentia pigmenti tumors  
Inflammatory linear verrucous epidermal nevus  
Keratoacanthoma  
Mucinous syringometaplasia  
Multicentric reticulohistiocytosis  
Onycholemmal horn  
Onychophosis affecting a lateral fold of toenail  
Solitary congenital nodular calcification of the skin  
Subungual corn (heloma)  
Subungual filamentous tumor  
Subungual vegetations of amyloidosis  
Tuberculosis cutis verrucosa  
Verruca vulgaris  
Verruciform xanthoma  
Verrucous epidermal nevus |
<table>
<thead>
<tr>
<th>Nail anatomical site</th>
<th>Onychopathy</th>
<th>Associated disease</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Lunula</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td><em>Color</em></td>
<td>Black</td>
<td>Infectious</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Chikungunya</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Drugs</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Sparfloxacin</td>
</tr>
<tr>
<td></td>
<td>Blue</td>
<td>Gastrointestinal</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Liver</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Wilson disease</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Orthopedic</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Myxoid pseudocyst</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Drugs</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Antimalarials</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Amodiaquine</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Chloroquine</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Mepacrine (quinacrine)</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Argyria</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Busulfan (busulphan)</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Phenolphthalein</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Sparfloxacin</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Zidovudine</td>
</tr>
<tr>
<td></td>
<td>Red</td>
<td>Idiopathic</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Congenital or hereditary</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Hereditary benign telangiectasia</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Cardiovascular</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Angina pectoris</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Conduction abnormalities</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Congestive heart failure</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Coronary atherosclerotic heart disease</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Fever-induced heart disease</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Hypertension</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Myocardial infarction</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Rheumatic heart disease</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Thyrotoxic heart disease</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Pulmonary</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Chronic bronchitis</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Chronic obstructive pulmonary disease</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Emphysema</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Gastrointestinal</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Esophageal strictures</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Hepatic</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Cirrhosis</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Irritable bowel syndrome</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Pyloric channel ulcers</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Renal</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Proteinuria</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Neurological</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Cerebrovascular accident</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Endocrine</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Diabetes</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Thyroid disease</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Hematological</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Anemia of chronic disease</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Idiopathic transient leukopenia</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Infections</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Lymphogranuloma venereum</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Pneumonia</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Tuberculosis</td>
</tr>
<tr>
<td>Nail anatomical site</td>
<td>Onychopathy</td>
<td>Associated disease</td>
</tr>
<tr>
<td>-----------------------------</td>
<td>-------------------</td>
<td>------------------------------------------------------------------------------------</td>
</tr>
<tr>
<td>Lunula (cont’d)</td>
<td>Red (cont’d)</td>
<td>Neoplastic</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Hodgkin disease</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Lymphoid follicular reticulosis</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Lymphosarcoma</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Myeloid leukemia</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Polycythemia vera</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Reticulosarcoma</td>
</tr>
<tr>
<td>Orthopedic</td>
<td></td>
<td>Baker’s cyst</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Myxoid pseudocyst</td>
</tr>
<tr>
<td>Rheumatological</td>
<td></td>
<td>Baker’s cyst</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Dermatomyositis</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Drug-induced lupus (procainamide)</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Osteoarthritis</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Polymyalgia rheumatica</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Rheumatoid arthritis</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Systemic lupus erythematosus</td>
</tr>
<tr>
<td>Dermatological</td>
<td></td>
<td>Alopecia areata</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Chronic urticaria</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Lichen planus (punctate redness)</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Lichen sclerosus et atrophicus</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Psoriasis</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Twenty-nail dystrophy</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Vitiligo</td>
</tr>
<tr>
<td>Malnutrition</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Drugs</td>
<td></td>
<td>Amoxicillin/clavulanic acid (subungual fixed drug eruption)</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Corticosteroid use</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Procainamide</td>
</tr>
<tr>
<td>Toxicity</td>
<td></td>
<td>Alcohol abuse</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Carbon monoxide poisoning</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Tobacco use</td>
</tr>
<tr>
<td>Trauma</td>
<td></td>
<td>Repeated microtrauma (habit tic)</td>
</tr>
<tr>
<td>Miscellaneous</td>
<td></td>
<td>Chronic idiopathic lymphedema</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Hay fever pollen desensitization</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Senile macular degeneration</td>
</tr>
<tr>
<td>Yellow</td>
<td>Drugs</td>
<td>Tetracycline (both on examination and produces yellow fluorescence with Wood’s light)</td>
</tr>
<tr>
<td>Shape</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Absence</td>
<td>Hereditary or congenital</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Focal dermal hypoplasia (Goltz–Gorlin syndrome)</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Nail–patella syndrome</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Pachyonychia congenita with leukonychia</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Soft nail disease</td>
<td></td>
</tr>
<tr>
<td>Renal</td>
<td></td>
<td>Hemodialysis</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Renal transplantation</td>
</tr>
<tr>
<td>Hematological</td>
<td></td>
<td>Erythropoietic porphyria</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Erythropoietic protoporphyrja</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Porphyria cutanea tarda</td>
</tr>
<tr>
<td>Metabolic</td>
<td></td>
<td>Histidinemia</td>
</tr>
<tr>
<td>Nail anatomical site</td>
<td>Onychopathy</td>
<td>Associated disease</td>
</tr>
<tr>
<td>----------------------</td>
<td>-------------</td>
<td>--------------------</td>
</tr>
<tr>
<td></td>
<td>Drugs</td>
<td>Penicillamine</td>
</tr>
<tr>
<td>Macrolunula</td>
<td>Idiopathic</td>
<td>Normal persons (e.g. in India)</td>
</tr>
<tr>
<td></td>
<td>Endocrine</td>
<td>Hyperthyroidism</td>
</tr>
<tr>
<td></td>
<td>Infectious</td>
<td>Leprosy</td>
</tr>
<tr>
<td></td>
<td>Dermatological</td>
<td>Median nail dystrophy</td>
</tr>
<tr>
<td></td>
<td>Drugs</td>
<td>Post application of hydrocortisone to cuticle</td>
</tr>
<tr>
<td></td>
<td>Trauma</td>
<td>Habit–tic deformity</td>
</tr>
<tr>
<td>Pseudomacrolunula</td>
<td>Infectious</td>
<td>Leprosy</td>
</tr>
<tr>
<td>Triangular lunula</td>
<td>Hereditary or congenital</td>
<td>Nail–patella syndrome</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Trisomy 21</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Trauma</td>
</tr>
</tbody>
</table>

### Nail bed

<table>
<thead>
<tr>
<th>Color</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>Black</td>
<td>Infectious</td>
</tr>
<tr>
<td></td>
<td>Pinta</td>
</tr>
<tr>
<td>Blue</td>
<td>Congenital or hereditary</td>
</tr>
<tr>
<td></td>
<td>Hereditary benign telangiectasia</td>
</tr>
<tr>
<td></td>
<td>Hereditary hemorrhagic telangiectasia (Rendu–Olser–Weber syndrome)</td>
</tr>
<tr>
<td></td>
<td>Telangiectasia hereditary hemorrhagic</td>
</tr>
<tr>
<td></td>
<td>Klippel–Trénaunay–Weber syndrome</td>
</tr>
<tr>
<td></td>
<td>Nigremia (hemoglobin M lymph disease)</td>
</tr>
<tr>
<td>Gastrointestinal</td>
<td>Hepatic</td>
</tr>
<tr>
<td></td>
<td>Wilson disease</td>
</tr>
<tr>
<td>Hematological</td>
<td>Pernicious anemia</td>
</tr>
<tr>
<td>Vascular</td>
<td>Venous malformations</td>
</tr>
<tr>
<td>Dermatological</td>
<td>Porphyria cutanea tarda</td>
</tr>
<tr>
<td>Drugs</td>
<td>Anamalerials</td>
</tr>
<tr>
<td></td>
<td>Amodiaquine</td>
</tr>
<tr>
<td></td>
<td>Chloroquine</td>
</tr>
<tr>
<td></td>
<td>Mepacrine (quinacrine)</td>
</tr>
<tr>
<td></td>
<td>Argyria</td>
</tr>
<tr>
<td></td>
<td>Minocycline</td>
</tr>
<tr>
<td></td>
<td>Phenothiazines</td>
</tr>
<tr>
<td></td>
<td>Quinidine (horizontal)</td>
</tr>
<tr>
<td>Toxicity</td>
<td>Aniline poisoning (purple-blue)</td>
</tr>
<tr>
<td>Miscellaneous</td>
<td>Angiolympoid hyperplasia with eosinophilia</td>
</tr>
<tr>
<td>Blue-red diffuse</td>
<td>Hereditary or congenital</td>
</tr>
<tr>
<td></td>
<td>Hereditary benign telangiectasia</td>
</tr>
<tr>
<td>Dermatological</td>
<td>Discoid lupus erythematosus</td>
</tr>
<tr>
<td>Nail anatomical site</td>
<td>Onychopathy</td>
</tr>
<tr>
<td>---------------------</td>
<td>-------------</td>
</tr>
<tr>
<td><strong>Nail bed</strong> (cont’d)</td>
<td>Brown diffuse</td>
</tr>
<tr>
<td>Color</td>
<td></td>
</tr>
<tr>
<td>Drugs</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
</tr>
<tr>
<td>Red</td>
<td>Erythronychia</td>
</tr>
<tr>
<td></td>
<td>Longitudinal</td>
</tr>
<tr>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
</tr>
<tr>
<td>Polydactylyous</td>
<td>Acantholytic dyskeratoses</td>
</tr>
<tr>
<td></td>
<td>Acrokeratosis verruciformis of Hopf</td>
</tr>
<tr>
<td></td>
<td>Amyloidosis</td>
</tr>
<tr>
<td></td>
<td>Celiac disease</td>
</tr>
<tr>
<td></td>
<td>Darier disease</td>
</tr>
<tr>
<td></td>
<td>Epidermolysis bullosa</td>
</tr>
<tr>
<td></td>
<td>Graft-versus-host disease</td>
</tr>
<tr>
<td></td>
<td>Lichen planus</td>
</tr>
<tr>
<td></td>
<td>Radiodermatitis (chronic)</td>
</tr>
<tr>
<td></td>
<td>Systemic amyloidosis</td>
</tr>
<tr>
<td></td>
<td>Tuberculous sclerosis</td>
</tr>
<tr>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>Renal</td>
</tr>
<tr>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
</tr>
<tr>
<td>Nail anatomical site</td>
<td>Onychopathy</td>
</tr>
<tr>
<td>---------------------</td>
<td>-------------</td>
</tr>
<tr>
<td></td>
<td>Metabolic</td>
</tr>
<tr>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>Drugs</td>
</tr>
<tr>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
</tr>
<tr>
<td>Red diffuse</td>
<td>Hereditary or congenital</td>
</tr>
<tr>
<td></td>
<td>Toxicity</td>
</tr>
<tr>
<td>Red punctate</td>
<td>Hereditary or congenital</td>
</tr>
<tr>
<td></td>
<td>Vascular</td>
</tr>
<tr>
<td></td>
<td>Neoplastic</td>
</tr>
<tr>
<td></td>
<td>Drug</td>
</tr>
<tr>
<td></td>
<td></td>
</tr>
<tr>
<td>Red transverse banding</td>
<td>Rheumatological</td>
</tr>
<tr>
<td></td>
<td>Drugs</td>
</tr>
<tr>
<td>Quincke's pulse</td>
<td>Cardiovascular</td>
</tr>
<tr>
<td>Splinter hemorrhage</td>
<td>Idiopathic</td>
</tr>
<tr>
<td></td>
<td>Physiological</td>
</tr>
<tr>
<td></td>
<td>Cardiovascular</td>
</tr>
<tr>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>Gastrointestinal</td>
</tr>
<tr>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>Renal</td>
</tr>
<tr>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>Neurological</td>
</tr>
<tr>
<td>Nail anatomical site</td>
<td>Onychopathy</td>
</tr>
<tr>
<td>-------------------------</td>
<td>--------------------------------------------</td>
</tr>
<tr>
<td>Nail bed (cont'd)</td>
<td>Red transverse banding (cont'd)</td>
</tr>
<tr>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
</tr>
<tr>
<td>Color</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
</tr>
<tr>
<td>Vascular</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
</tr>
<tr>
<td>Infectious</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
</tr>
<tr>
<td>Neoplastic</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
</tr>
<tr>
<td>Rheumatological</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
</tr>
<tr>
<td>Vasculitis</td>
<td></td>
</tr>
<tr>
<td>Dermatological</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
</tr>
<tr>
<td>Malnutrition</td>
<td></td>
</tr>
</tbody>
</table>
## Appendix

<table>
<thead>
<tr>
<th>Nail anatomical site</th>
<th>Onychopathy</th>
<th>Associated disease</th>
</tr>
</thead>
<tbody>
<tr>
<td>Drug</td>
<td>Antivascular endothelial growth factor receptor (VEGFR) drugs</td>
<td>Terbinafine</td>
</tr>
<tr>
<td>Drug</td>
<td>Atenolol</td>
<td>Tetracycline</td>
</tr>
<tr>
<td>Drug</td>
<td>Ganciclovir</td>
<td></td>
</tr>
<tr>
<td>Drug</td>
<td>Griseofulvin</td>
<td></td>
</tr>
<tr>
<td>Drug</td>
<td>Ketoconazole</td>
<td></td>
</tr>
<tr>
<td>Drug</td>
<td>Psoralens and PUVA</td>
<td></td>
</tr>
<tr>
<td>Drug</td>
<td>Sorafenib</td>
<td></td>
</tr>
<tr>
<td>Drug</td>
<td>Sunitinib</td>
<td></td>
</tr>
<tr>
<td>Drug</td>
<td>Terbinafine</td>
<td></td>
</tr>
<tr>
<td>Drug</td>
<td>Tetracycline</td>
<td></td>
</tr>
<tr>
<td>Trauma</td>
<td>Golfers nails, especially in golf grip hand</td>
<td>Amyloidosis</td>
</tr>
<tr>
<td>Trauma</td>
<td>Harp playing</td>
<td>Hyperesinophilic syndrome</td>
</tr>
<tr>
<td>Trauma</td>
<td>Light trauma</td>
<td>Irradiation</td>
</tr>
<tr>
<td>Trauma</td>
<td>Pen push purpura in comatose patients</td>
<td>Sarcoidosis</td>
</tr>
<tr>
<td>Trauma</td>
<td>Tennis, soccer, jogging, in toenails</td>
<td></td>
</tr>
<tr>
<td>Miscellaneous</td>
<td>Golfer's nails, especially in golf grip hand</td>
<td></td>
</tr>
<tr>
<td>Miscellaneous</td>
<td>Harp playing</td>
<td></td>
</tr>
<tr>
<td>Miscellaneous</td>
<td>Light trauma</td>
<td></td>
</tr>
<tr>
<td>Miscellaneous</td>
<td>Pen push purpura in comatose patients</td>
<td></td>
</tr>
<tr>
<td>Miscellaneous</td>
<td>Tennis, soccer, jogging, in toenails</td>
<td></td>
</tr>
<tr>
<td>miscellaneous</td>
<td>Amyloidosis</td>
<td></td>
</tr>
<tr>
<td>miscellaneous</td>
<td>Hyperesinophilic syndrome</td>
<td></td>
</tr>
<tr>
<td>miscellaneous</td>
<td>Irradiation</td>
<td></td>
</tr>
<tr>
<td>miscellaneous</td>
<td>Sarcoidosis</td>
<td></td>
</tr>
</tbody>
</table>

### Terry's nail

<table>
<thead>
<tr>
<th>Idiopathic</th>
<th>Old age</th>
<th>amiodarone</th>
</tr>
</thead>
<tbody>
<tr>
<td>Idiopathic</td>
<td>Young children and young adults</td>
<td>Itraconazole</td>
</tr>
<tr>
<td>Idiopathic</td>
<td>Hereditary or congenital</td>
<td>Vincristine</td>
</tr>
<tr>
<td>Idiopathic</td>
<td>Citrullinemia</td>
<td></td>
</tr>
<tr>
<td>Cardiovascular disease</td>
<td>Congestive heart failure</td>
<td></td>
</tr>
<tr>
<td>Pulmonary</td>
<td>Pulmonary eosinophilia</td>
<td></td>
</tr>
<tr>
<td>Pulmonary</td>
<td>Pulmonary tuberculosis</td>
<td></td>
</tr>
<tr>
<td>Gastrointestinal</td>
<td>Hepatic</td>
<td></td>
</tr>
<tr>
<td>Gastrointestinal</td>
<td>Cirrhosis</td>
<td></td>
</tr>
<tr>
<td>Gastrointestinal</td>
<td>Convalescent hepatitis</td>
<td></td>
</tr>
<tr>
<td>Endocrine</td>
<td>Ulcerative colitis</td>
<td></td>
</tr>
<tr>
<td>Endocrine</td>
<td>Diabetes mellitus</td>
<td></td>
</tr>
<tr>
<td>Endocrine</td>
<td>POEMS syndrome</td>
<td></td>
</tr>
<tr>
<td>Endocrine</td>
<td>Thyrotoxicosis</td>
<td></td>
</tr>
<tr>
<td>Hematological</td>
<td>Blood disorders</td>
<td></td>
</tr>
<tr>
<td>Hematological</td>
<td>Infectious</td>
<td></td>
</tr>
<tr>
<td>Hematological</td>
<td>Leprosy</td>
<td></td>
</tr>
<tr>
<td>Neoplastic</td>
<td>Neoplasm</td>
<td></td>
</tr>
<tr>
<td>Neoplastic</td>
<td>Carcinoma</td>
<td></td>
</tr>
<tr>
<td>Neoplastic</td>
<td>Pancreatic carcinoma with hepatic metastasis</td>
<td></td>
</tr>
<tr>
<td>Neoplastic</td>
<td>Plasmacytoma</td>
<td></td>
</tr>
<tr>
<td>Rheumatological</td>
<td>Reiter syndrome</td>
<td></td>
</tr>
<tr>
<td>Rheumatological</td>
<td>Rheumatoid arthritis</td>
<td></td>
</tr>
<tr>
<td>Dermatological</td>
<td>Actinic keratosis</td>
<td></td>
</tr>
<tr>
<td>Malnutrition</td>
<td>Drugs (prominent onychodermal band)</td>
<td></td>
</tr>
<tr>
<td>Malnutrition</td>
<td>Cyclophosphamide</td>
<td></td>
</tr>
<tr>
<td>Malnutrition</td>
<td>Itraconazole</td>
<td></td>
</tr>
<tr>
<td>Malnutrition</td>
<td>Vincristine</td>
<td></td>
</tr>
<tr>
<td>Malnutrition</td>
<td>Drugs (prominent onychodermal band)</td>
<td></td>
</tr>
<tr>
<td>Nail anatomical site</td>
<td>Onychopathy</td>
<td>Associated disease</td>
</tr>
<tr>
<td>--------------------------</td>
<td>-----------------</td>
<td>-----------------------------------------------------------------------------------</td>
</tr>
<tr>
<td><strong>Nail bed (cont’d)</strong></td>
<td></td>
<td><strong>White</strong></td>
</tr>
<tr>
<td><em>Color</em></td>
<td></td>
<td>Muehrcke’s lines</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Cardiovascular disease</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Post heart transplantation surgery</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Gastrointestinal</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Hepatic disease</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Renal</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Glomerulonephritis</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Hypoalbuminemia</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Hypoalbuminemia and normal serum albumin</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Nephrotic syndrome</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Malnutrition</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Acrodermatitis enteropathica</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Drugs</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Chemotherapeutic agents</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Post trauma</td>
</tr>
<tr>
<td><strong>Yellow</strong></td>
<td></td>
<td><strong>Oil-dropping sign</strong></td>
</tr>
<tr>
<td></td>
<td></td>
<td>Hereditary or congenital</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Osteopoikilosis: Buschke–Ollendorff syndrome</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Rheumatological</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Systemic lupus erythematosus</td>
</tr>
<tr>
<td></td>
<td></td>
<td><strong>Dermatological</strong></td>
</tr>
<tr>
<td></td>
<td></td>
<td>Acrokeratosis verruciformis of Hopf</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Darier disease</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Epidermolysis bullosa</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Hailey–Hailey disease</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Tumor of the matrix or nail bed</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Warty dyskeratoma</td>
</tr>
<tr>
<td><strong>Shape</strong></td>
<td></td>
<td><strong>Onycholyis</strong></td>
</tr>
<tr>
<td></td>
<td></td>
<td>Idiopathic</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Leukoonycholysis paradentotica</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Hereditary or congenital</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Congenital ectodermal defect</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Congenital ingrown toenails</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Congenital onycholyis</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Dysplasia of the fifth toenail</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Ectodermal dysplasia, alopecia, onychodysplasia, hypohidrosis, keratoderma, abnormal teeth and deafness</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Ectodermal dysplasia, hidrotic, Clouston syndrome</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Epidermolysis bullosa</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Junctional, late onset</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Simplex, localized</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Simplex with hyperpigmentation, palmoplantar keratosis</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Hair and nail dysplasia</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Hereditary nail dysplasia of the fifth toe</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Hereditary partial onycholyis</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Hidrotic ectodermal dysplasia</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Hyperpigmentation and hypohidrosis</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Hyperpigmentation, hypotrichosis and dystrophy of nails. Naegeli–Franceschetti– Jadassohn syndrome</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Hypoplastic enamel, onycholysis, and hypohidrosis</td>
</tr>
<tr>
<td>Nail anatomical site</td>
<td>Onychopathy</td>
<td>Associated disease</td>
</tr>
<tr>
<td>---------------------</td>
<td>-------------</td>
<td>--------------------</td>
</tr>
<tr>
<td>Idiopathic acquired onycholysis</td>
<td>Leprechaunism</td>
<td>Malalignment of the big toenail</td>
</tr>
<tr>
<td>Malalignment of the big toenail</td>
<td>Osteopoikilosis: Buschke–Ollendorff syndrome</td>
<td>Pachyonychia congenita type 1 of Jadassohn–Lewandowsky</td>
</tr>
<tr>
<td>Pachyonychia congenita with leukonychia</td>
<td>Periodic shedding</td>
<td>Schöpf–Schulz–Passarge syndrome</td>
</tr>
<tr>
<td>Palmoplantar keratoderma with cystic eyelids, hypodontia, and hypotrichosis</td>
<td>Speckled hyperpigmentation, palmoplantar punctate keratoses, and childhood blistering</td>
<td></td>
</tr>
<tr>
<td>Physiological</td>
<td>Pregnancy</td>
<td>Gastrointestinal</td>
</tr>
<tr>
<td>Cronkhite–Canada syndrome</td>
<td>Renal</td>
<td>Hemodialysis (photo-onycholysis)</td>
</tr>
<tr>
<td>Endocrine</td>
<td>Diabetes</td>
<td>Thyroid disease</td>
</tr>
<tr>
<td>Thyroid disease</td>
<td>Hematological</td>
<td>Iron deficiency anemia</td>
</tr>
<tr>
<td>Porphyria</td>
<td>Bantu porphyria</td>
<td>Erythropoietic porphyria</td>
</tr>
<tr>
<td>Erythropoietic protoporphyria</td>
<td>Porphyria cutanea tarda</td>
<td>Pseudoporphyria</td>
</tr>
<tr>
<td>Variegate porphyria</td>
<td>Vascular</td>
<td>Acrocyanosis</td>
</tr>
<tr>
<td>Impaired circulation</td>
<td>Ischemia</td>
<td>Raynaud syndrome</td>
</tr>
<tr>
<td>Infectious</td>
<td>AIDS</td>
<td>Exogenous</td>
</tr>
<tr>
<td>Exogenous</td>
<td>Bacteria</td>
<td>Candida spp.</td>
</tr>
<tr>
<td>Dermatophyte</td>
<td>Leprosy</td>
<td>Malassezia spp.</td>
</tr>
<tr>
<td>Scytalidium dimidiatum</td>
<td>Scytalidium hyalinum</td>
<td>Viral</td>
</tr>
<tr>
<td>HIV</td>
<td>Syphilis</td>
<td>Neoplastic</td>
</tr>
<tr>
<td>Bowen squamous cell carcinoma in situ</td>
<td>Carcinoma of the lung</td>
<td>Epithelioma (carcinoma) cuniculatum</td>
</tr>
<tr>
<td>Sclerotic fibroma</td>
<td>Squamous cell carcinoma</td>
<td>Squamous cell carcinoma of the lung</td>
</tr>
<tr>
<td>Syringoma</td>
<td>Rheumatological</td>
<td>Reactive arthritis</td>
</tr>
<tr>
<td>Rheumatoid arthritis</td>
<td>Systemic lupus erythematosus</td>
<td>Systemic sclerosis</td>
</tr>
</tbody>
</table>
### Nail anatomical site

<table>
<thead>
<tr>
<th>Nail bed (cont'd)</th>
<th>Onychopathy (cont'd)</th>
<th>Associated disease</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Nail bed</strong></td>
<td><strong>Onycholysis</strong></td>
<td>Dermatological</td>
</tr>
<tr>
<td><strong>Shape</strong></td>
<td></td>
<td>Acrokeratoelastoidosis</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Alopecia areata</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Bullous disease</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Contact dermatitis, e.g. alstroemia, rhus, acrylates, foods, hydroxylamine, formaldehyde resin, coelomic fluid of a sea-worm (<em>Nereis diversicolor</em>), aminehydroxylamine-containing soldering flux, ammonium thioglycolate, enzyme detergents, gold potassium cyanide</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Dermatitis</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Erythema elevatum diutinum</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Histiocytosis X</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Hyperhidrosis</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Keratosis lichenoides chronic</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Lichen planus</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Lichen striatus</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Multicentric reticulohistiocytosis</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Pachyonychia congenita</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Palmoplantar keratoderma, punctate</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Parakeratosis pustulosa</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Pemphigoid</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Pemphigus vegetans</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Psoriasis</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Reiter syndrome</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Shell nail syndrome</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Tumors of the nail bed</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Bowen disease</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Mycosis fungoides</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Pyogenic granuloma</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Yellow nail syndrome</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Occupational/external environment</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Exogenous</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Chemicals</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Maceration</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Nail cosmetics</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Occupational</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Local causes</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Exposure to chemicals or water</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Exposure to nail cosmetics</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Foreign body, e.g. glass spicules</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Harp playing</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Microwaves</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Radiation dermatitis (chronic)</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Thermal injury</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Trauma</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Malnutrition</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Pellagra</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Drugs</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Non-photo-induced</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Benoxaprofen (in toes)</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Captopril</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Chemotherapeutic agents</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Bleomycin</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Doxorubicin (Adriamycin)</td>
</tr>
<tr>
<td></td>
<td></td>
<td>5-Fluorouracil</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Hydroxyurea</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Paclitaxel</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Chloramphenicol</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Clofazimine</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Docetaxel</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Etretinate</td>
</tr>
<tr>
<td>Nail anatomical site</td>
<td>Onychopathy</td>
<td>Associated disease</td>
</tr>
<tr>
<td>---------------------</td>
<td>-------------</td>
<td>--------------------</td>
</tr>
<tr>
<td>Gold</td>
<td></td>
<td>Isotretinoin</td>
</tr>
<tr>
<td>Methotrexate</td>
<td></td>
<td>Methotrexate/leucovorin</td>
</tr>
<tr>
<td>Mitoxantrone</td>
<td></td>
<td>Mitoxantrone (usually great toenail)</td>
</tr>
<tr>
<td>Practolol</td>
<td></td>
<td>Paclitaxel</td>
</tr>
<tr>
<td>Protease inhibitors</td>
<td></td>
<td>Selenium intoxication</td>
</tr>
<tr>
<td>Tetracycline</td>
<td></td>
<td>Topical 5-fluorouracil</td>
</tr>
<tr>
<td>Valproic acid</td>
<td></td>
<td>Photo-induced</td>
</tr>
<tr>
<td>Acriflavine</td>
<td></td>
<td>Allopurinol</td>
</tr>
<tr>
<td>Antipsychotics</td>
<td></td>
<td>Aripiprazole</td>
</tr>
<tr>
<td>Olanzapine</td>
<td></td>
<td>Benoxaprofen</td>
</tr>
<tr>
<td>Captopril</td>
<td></td>
<td>Cefaloridine</td>
</tr>
<tr>
<td>Cefaloridine</td>
<td></td>
<td>Chloramphenicol</td>
</tr>
<tr>
<td>Chlorzepate</td>
<td></td>
<td>Chlorpromazine</td>
</tr>
<tr>
<td>Cloxacillin</td>
<td></td>
<td>Fluoroquinolones</td>
</tr>
<tr>
<td>Moxifloxacin</td>
<td></td>
<td>Sparfloxacin</td>
</tr>
<tr>
<td>Icodextrin</td>
<td></td>
<td>Indapamide</td>
</tr>
<tr>
<td>Indometacin</td>
<td></td>
<td>Methyl aminolevulinate</td>
</tr>
<tr>
<td>Oral contraceptives</td>
<td></td>
<td>Paroxetine</td>
</tr>
<tr>
<td>Phenothiazines</td>
<td></td>
<td>Psoralens and UVA or sunlight</td>
</tr>
<tr>
<td>Flumequine</td>
<td></td>
<td>8-methoxypsoralen</td>
</tr>
<tr>
<td>Ofloxacin</td>
<td></td>
<td>5-methoxypsoralen</td>
</tr>
<tr>
<td>Pefloxacin</td>
<td></td>
<td>Trimethylpsoralen</td>
</tr>
<tr>
<td>Sirolimus</td>
<td></td>
<td>Quinine sulfate</td>
</tr>
<tr>
<td>Quinolones</td>
<td></td>
<td>Quinolones</td>
</tr>
<tr>
<td>Flumequine</td>
<td></td>
<td>Ofloxacin</td>
</tr>
<tr>
<td>Pefloxacin</td>
<td></td>
<td>Pefloxacin</td>
</tr>
<tr>
<td>Tetracycline</td>
<td></td>
<td>Sirolimus</td>
</tr>
<tr>
<td>Chlortetracycline</td>
<td></td>
<td>Tetracycline</td>
</tr>
<tr>
<td>Demethylchlortetracycline</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Doxycycline</td>
<td></td>
<td>Minocycline</td>
</tr>
<tr>
<td>Oxytetracycline</td>
<td></td>
<td>Oxytetracycline</td>
</tr>
<tr>
<td>Tetracycline</td>
<td></td>
<td>Thiazide diuretics</td>
</tr>
<tr>
<td>Trypaflavine</td>
<td></td>
<td>Vogalene</td>
</tr>
<tr>
<td>Trauma</td>
<td></td>
<td>Thermal injury</td>
</tr>
<tr>
<td>Trauma</td>
<td></td>
<td>Miscellaneous</td>
</tr>
<tr>
<td>Amyloidosis</td>
<td></td>
<td>Asymmetric gait unit syndrome (AGNUS)</td>
</tr>
<tr>
<td>Graft-versus-host disease</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Nail anatomical site</td>
<td>Onychopathy</td>
<td>Associated disease</td>
</tr>
<tr>
<td>---------------------</td>
<td>-------------</td>
<td>--------------------</td>
</tr>
<tr>
<td><strong>Nail bed (cont'd)</strong></td>
<td>Onycholysis (cont'd)</td>
<td>Sarcoid</td>
</tr>
<tr>
<td><strong>Shape</strong></td>
<td></td>
<td>Shell nail syndrome</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Yellow nail syndrome</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Hereditary or congenital</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Acrokeratosis verruciformis (Hopf disease)</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Congenital ichthyosiform erythroderma</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Ectodermal dysplasia, alopecia, onychodysplasia, hypohidrosis, keratoderma, abnormal teeth and deafness</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Ectodermal dysplasia, hidrotic (Clouston syndrome)</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Epidermodyplasia verruciformis-like dermatoses</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Hyperpigmentation, hypotrichosis, and dystrophy of nails (Naegeli–Franceschetti–Jadassohn syndrome)</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Hypohidrotic ectodermal dysplasia</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Hypoplastic enamel, onycholysis, and hypohidrosis</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Keratoderma palmoplantar and alopecia</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Keratoderma palmoplantar progressiva of Meleda</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Keratoderma palmoplantar punctate type 1, keratoderma palmoplantar is papulosa of Buschke–Fischer</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Keratosis focal palmoplantar and gingival</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Olmsted syndrome</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Pachyonychia congenita type 2 of Jackson and Lawler</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Popliteal pterygium syndrome (Klein syndrome)</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Rapp–Hodgkin syndrome</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Tay syndrome or IBDS (ichthyotic, brittle hair, decreased fertility, short stature) or photosensitive trichothiodystrophy</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Trichothiodystrophy</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Physiological</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Pregnancy</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Vascular</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Acrocyanosis</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Infectious</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Dermatophyte</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Scabies</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Neoplastic</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Keratotic tumor</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Eccrine syringofibroadenoma</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Incontinentia pigmenti tumors</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Keratoacanthoma</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Koenen periungual fibromas</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Squamous cell carcinoma</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Subungual epidermoid inclusion</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Subungual linear keratotic melanonychia</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Subungual myxoid pleomorphic fibroma</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Subungual onycholemmal cyst</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Ungual seborrheic keratosis</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Verruca vulgaris</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Systemic</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Langerhans cell histiocytosis</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Sézary syndrome</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Rheumatological</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Kawasaki disease</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Systemic lupus erythematosus</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Dermatological</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Contact dermatitis, e.g. to cement, codeine sensitization in pharmaceutical workers, formaldehyde resin, resin cements, bryozoan invertebrates (“moss animals”)</td>
</tr>
<tr>
<td>Nail anatomical site</td>
<td>Onychopathy</td>
<td>Associated disease</td>
</tr>
<tr>
<td>---------------------</td>
<td>-------------</td>
<td>--------------------</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Darier disease</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Discoid lupus erythematosus</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Eczema</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Keratosis lichenoides chronica</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Incontinentia pigmenti</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Langerhans cell histiocytosis</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Lichen planus</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Lichen striatus</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Palmoplantar keratoderma, diffuse</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Palmoplantar keratoderma, punctate</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Parakeratosis pustulosa</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Pemphigoid</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Pityriasis rubra pilaris</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Psoriasis</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Reiter syndrome</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Subungual onycholemmal cyst</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Turpentine dermatitis</td>
</tr>
<tr>
<td>Drugs</td>
<td></td>
<td>Clofazimine</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Practolol</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Topical corticosteroids</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Venlafaxine</td>
</tr>
<tr>
<td>Toxicity</td>
<td></td>
<td>Lead intoxication</td>
</tr>
<tr>
<td>Miscellaneous</td>
<td></td>
<td>Sarcoïd</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Trauma</td>
</tr>
</tbody>
</table>

**Hyponychium**

**Color**
- Red
- Tuft erythema

**Shape**
- Pterygium inversum
- unguis (ventral pterygium)

**Cardiovascular**
- Congenital heart disease

**Idiopathic**
- Acquired idiopathic
- Hereditary or congenital
- Congenital idiopathic
- Familial

**Neurological**
- Causalgia of the median nerve
- Cerebrovascular accident
- Neurofibromatosis
- Paresis

**Vascular**
- Raynaud phenomenon and disease
- Vasospasm

**Infectious**
- Leprosy

**Orthopedic**
- Subungual exostosis

**Rheumatological**
- Dermatomyositis
- Systemic lupus erythematosus
- Systemic sclerosis

**Occupational/external environment**
- Formaldehyde-containing nail hardeners

**Drugs**
- Beta blockers
<table>
<thead>
<tr>
<th>Nail anatomical site</th>
<th>Onychopathy</th>
<th>Associated disease</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Hyponychium</strong> (cont’d) <strong>Shape</strong></td>
<td>Red (cont’d)</td>
<td>Trauma</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Conditions that lead to local scarring</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Miscellaneous</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Lenticular atrophy of the palmar creases</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Sarcoid</td>
</tr>
<tr>
<td><strong>Tumor</strong></td>
<td>Neoplastic</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Smooth</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Koenen periungual fibromas</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Leiomyoma</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Metastasis</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Mucinous adenocystic sweat gland carcinoma</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Pyogenic granuloma</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Verrucous</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Distal subungual fibrokeratoma</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Distal subungual keratosis</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Epithelioma (carcinoma) cuniculatum</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Incontinentia pigmenti tumors</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Keratoacanthoma</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Malignant proliferating onycholemmal cyst</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Onychopapilloma (distal portion)</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Squamous cell carcinoma</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Verruca vulgaris</td>
<td></td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Nail plate <strong>Color</strong></th>
<th><strong>Blue</strong></th>
<th><strong>Drugs</strong></th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td>Amorolfine</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Cupric sulfate</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Mercury bichloride</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Methylene blue</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th></th>
<th><strong>Brown</strong></th>
<th><strong>Diffuse</strong></th>
<th>Hereditary or congenital</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td></td>
<td>Acanthosis nigricans</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>Acrodermatitis enteropathica</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>Aplasia cutis with dystrophic nails</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>Congenital phenytoin effect</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>Congenital pigmented nevi of the nails</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>Congenital porphyria (Günther)</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>Ectodermal dysplasia syndromes</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>Epidermal nevus</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>Macular amyloidosis with familial nail</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>Pachyonychia congenita</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>Porphyria cutanea tarda</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>Renal</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>Hyperbilirubinemia</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>Hematological</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>Erythropoietic porphyria</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>Erythropoietic protoporphyria</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>Hemochromatosis</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>Porphyria cutanea tarda</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>Infectious</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>AIDS</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>Chikungunya</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>Rheumatological</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>Rheumatoid arthritis</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>Systemic lupus erythematosus</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>Malnutrition</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>Malnutrition</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>Vitamin B12 deficiency</td>
</tr>
</tbody>
</table>
### Nail anatomical site

- Onychopathy
- Associated disease

#### Drugs
- Abacavir
- Ammoniated mercury
- Amorolfine (topical use)
- Carbamazepine
- Chemotherapeutic agents
  - Bleomycin
  - Capecitabine
  - Cyclophosphamide
  - Dacarbazine
  - Daunorubicin
  - Docetaxel
  - Doxorubicin (Adriamycin)
  - Etoposide
  - 5-Fluorouracil
  - Hydroxyurea
  - Ifosfamide
  - Melphalan
  - Methotrexate
  - Nitrogen mustard
  - Nitrosourea
  - Paclitaxel
  - Tegafur
  - Clofazimine
  - Dilantin
- Epidermal growth factor receptor inhibitors
- Ethacridine
- Glutaraldehyde
- Gold
- Hydantoin
- Hydroquinone (topical)
- Iodochlorhydroxyquinolone
- Losartan, valsartan
- Minocycline
- Mitoxantrone
- Potassium permanganate
- Practolol
- Protease inhibitors
  - Abacavir
  - Indinavir
  - Lamivudine
  - Ritonavir
- Psoralens and PUVA (proximal plate)
- Pyrogallol
- Retigabine
- Resorcin
- Roxithromycin
- Timolol maleate 0.5% eye drops
- X-ray therapy
- Zidovudine

#### Toxicity
- Arsenic intoxication
- Iron (exogenous exposure to water with high iron)
- Lead intoxication
- Mercury intoxication
- Polychlorinated biphenyl intoxication
- Thallium poisoning

#### Miscellaneous
- Henna
- Hydroquinone
- Iron
- Nicotine
<table>
<thead>
<tr>
<th>Nail anatomical site</th>
<th>Onychopathy</th>
<th>Associated disease</th>
</tr>
</thead>
<tbody>
<tr>
<td>Nail plate (cont’d)</td>
<td>Brown (cont’d)</td>
<td>Multicentric reticulohistiocytosis</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Radiotherapy</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Thermal injury</td>
</tr>
<tr>
<td></td>
<td>Longitudinal</td>
<td>Single band</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Non-neoplastic</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Carpal tunnel syndrome</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Foreign body</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Hematoma</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Irradiation</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Postinflammatory hyperpigmentation</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Trauma, nail biting, frictional</td>
</tr>
<tr>
<td></td>
<td>Neoplastic</td>
<td>Melanocytic</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Acquired nevus</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Congenital nevus</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Lentigo</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Proliferation of normal melanocytes</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Proliferation of atypical melanocytes</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Postoperative</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Melanoma</td>
</tr>
<tr>
<td></td>
<td></td>
<td>In situ</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Metastatic</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Subungual</td>
</tr>
<tr>
<td></td>
<td>Non-melanocytic</td>
<td>Basal cell carcinoma</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Bowen squamous cell carcinoma in situ</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Fibrokeratoma</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Fibroma</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Histioctyoma</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Linear pigmented subungual keratosis</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Myxoid cyst</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Onychomatricoma</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Onychopapilloma</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Squamous cell carcinoma</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Subungual fibrous histioctyoma</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Subungual linear keratotic melanonychia</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Verruca vulgaris</td>
</tr>
<tr>
<td></td>
<td>Multiple bands</td>
<td>Non-neoplastic</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Hereditary</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Racial variation</td>
</tr>
<tr>
<td></td>
<td></td>
<td>African-American</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Hispanic</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Indian and other dark-skinned races</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Japanese</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Physiological</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Pregnancy</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Gastrointestinal</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Peutz–Jeghers syndrome</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Renal</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Hyperbilirubinemia</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Endocrine</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Addison disease</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Adrenalecmy for Cushing disease</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Hyperthyroidism</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Hematological</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Hemosiderosis</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Porphyria cutanea tarda</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Infectious</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Microbial</td>
</tr>
<tr>
<td>Nail anatomical site</td>
<td>Onychopathy</td>
<td>Associated disease</td>
</tr>
<tr>
<td>----------------------</td>
<td>-------------</td>
<td>--------------------</td>
</tr>
<tr>
<td>AIDS</td>
<td>Acrothecium nigrum</td>
<td>Alternaria spp.</td>
</tr>
<tr>
<td></td>
<td>Alternaria spp.</td>
<td>Aureobasidium pullulans</td>
</tr>
<tr>
<td></td>
<td>Bacteria</td>
<td>Blastomyces spp.</td>
</tr>
<tr>
<td></td>
<td>Candida spp.</td>
<td>Chaetomium spp.</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Cladosporium spp.</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Curvularia lunata</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Fusarium spp.</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Hendersonula toruloidea</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Hormodendrum elatum</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Phialophora spp.</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Phyllosticta sydowii</td>
</tr>
<tr>
<td></td>
<td>Pinta</td>
<td>Proteus mirabilis</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Scopulariopsis bireumptii</td>
</tr>
<tr>
<td></td>
<td>Secondary syphilis</td>
<td>T. mentagrophytes var. mentagrophytes</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Trichophyton rubrum</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Trichophyton soudanense</td>
</tr>
<tr>
<td></td>
<td>Microbial immunodeficiency</td>
<td>Rheumatological</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Systemic lupus erythematosus</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Dermatological</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Laugier–Hunziker–Baran syndrome</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Lichen planus</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Lichen striatus</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Prurigo vulgaris</td>
</tr>
<tr>
<td></td>
<td>Malnutrition</td>
<td>Malnutrition</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Vitamin B12 deficiency</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Vitamin D deficiency</td>
</tr>
<tr>
<td></td>
<td>Drugs and ingestants</td>
<td>Drugs and ingestants</td>
</tr>
<tr>
<td></td>
<td>Amlodipine</td>
<td>Amlodipine</td>
</tr>
<tr>
<td></td>
<td>Antimarialials</td>
<td>Antimarialials</td>
</tr>
<tr>
<td></td>
<td>Arsenic intoxication</td>
<td>Arsenic intoxication</td>
</tr>
<tr>
<td></td>
<td>Bleomycin</td>
<td>Bleomycin</td>
</tr>
<tr>
<td></td>
<td>Busulfan</td>
<td>Busulfan</td>
</tr>
<tr>
<td></td>
<td>Chemotherapeutic agents</td>
<td>Chemotherapeutic agents</td>
</tr>
<tr>
<td></td>
<td>Bleomycin</td>
<td>Bleomycin</td>
</tr>
<tr>
<td></td>
<td>Cyclophosphamide</td>
<td>Cyclophosphamide</td>
</tr>
<tr>
<td></td>
<td>Doxorubicin (Adriamycin)</td>
<td>Doxorubicin (Adriamycin)</td>
</tr>
<tr>
<td></td>
<td>5-Fluorouracil</td>
<td>5-Fluorouracil</td>
</tr>
<tr>
<td></td>
<td>Hydroxyurea</td>
<td>Hydroxyurea</td>
</tr>
<tr>
<td></td>
<td>Melphalan</td>
<td>Melphalan</td>
</tr>
<tr>
<td></td>
<td>Methotrexate</td>
<td>Methotrexate</td>
</tr>
<tr>
<td></td>
<td>Nitrogen mustard</td>
<td>Nitrogen mustard</td>
</tr>
<tr>
<td></td>
<td>Nitrosourea</td>
<td>Nitrosourea</td>
</tr>
<tr>
<td></td>
<td>Diquat</td>
<td>Diquat</td>
</tr>
<tr>
<td></td>
<td>Carbamazepine</td>
<td>Carbamazepine</td>
</tr>
<tr>
<td></td>
<td>Dilantin</td>
<td>Dilantin</td>
</tr>
<tr>
<td></td>
<td>Fluconazole</td>
<td>Fluconazole</td>
</tr>
<tr>
<td></td>
<td>Fluoride</td>
<td>Fluoride</td>
</tr>
<tr>
<td></td>
<td>5-Fluorouracil</td>
<td>5-Fluorouracil</td>
</tr>
<tr>
<td></td>
<td>Gold</td>
<td>Gold</td>
</tr>
<tr>
<td></td>
<td>Hydantoin</td>
<td>Hydantoin</td>
</tr>
<tr>
<td></td>
<td>Ibuprofen</td>
<td>Ibuprofen</td>
</tr>
<tr>
<td></td>
<td>Interferon alfa</td>
<td>Interferon alfa</td>
</tr>
<tr>
<td>Nail anatomical site</td>
<td>Onychopathy</td>
<td>Associated disease</td>
</tr>
<tr>
<td>---------------------</td>
<td>-------------</td>
<td>--------------------</td>
</tr>
<tr>
<td><strong>Nail plate</strong> (cont’d)</td>
<td>Brown (cont’d)</td>
<td>Ketoconazole, Lamivudine, Mepacrine, Mercury, Minocycline, Phenytoin, Phenothiazine, Psoralen and PUVA, Roxithromycin, Sulfonamides, Tetracycline, Timolol, UVB and UVA phototherapy, Zidovudine</td>
</tr>
<tr>
<td><strong>Color</strong></td>
<td></td>
<td>Irradiation, Neoplastic, Breast cancer</td>
</tr>
<tr>
<td><strong>Transverse</strong></td>
<td>Infectious</td>
<td>AIDS, Malaria, Rheumatological, Kawasaki disease, Malnutrition, Vitamin B12 deficiency</td>
</tr>
<tr>
<td></td>
<td>Drugs</td>
<td>Adrenocorticotropic hormone (ACTH), Chemotherapeutic agents, Bleomycin, 5-Bromodeoxyuridine and radiation, Cyclophosphamide, Daunorubicin, Doxorubicin (Adriamycin), 5-fluorouracil, Hydroxyurea, Nitrogen mustard, Nitrosourea, Electron beam, Lithium, Melanocyte-stimulating hormone, Prednisone, Zidovudine, Miscellaneous, Cryotherapy</td>
</tr>
<tr>
<td><strong>Green</strong></td>
<td>Infectious</td>
<td><em>Pseudomonas</em></td>
</tr>
<tr>
<td></td>
<td>Drugs</td>
<td>Chrysarobin, Methylene blue, Potassium permanganate</td>
</tr>
<tr>
<td><strong>Grey</strong></td>
<td>Drugs</td>
<td>Formaldehyde, Hydroquinone, Mercury bichloride</td>
</tr>
<tr>
<td><strong>Orange</strong></td>
<td>Drugs</td>
<td>Anthralin, Arning’s tincture, Iodochlorohydroxyquinolone</td>
</tr>
<tr>
<td>Nail anatomical site</td>
<td>Onychopathy</td>
<td>Associated disease</td>
</tr>
<tr>
<td>---------------------</td>
<td>-------------</td>
<td>--------------------</td>
</tr>
<tr>
<td>Purple</td>
<td>Drugs</td>
<td>Miscellaneous</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Hydroquinone</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Nail varnish</td>
</tr>
<tr>
<td>White</td>
<td>Hereditary or congenital</td>
<td>Bart–Pumphrey syndrome, palmoplantar keratoderma with leukonychia, deafness Longitudinal pachyleukonychia</td>
</tr>
<tr>
<td>Leukonychia</td>
<td></td>
<td>Neoplastic</td>
</tr>
<tr>
<td>Longitudinal</td>
<td></td>
<td>Epidermal hamartoma</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Nevoid matrix change</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Onychopapilloma</td>
</tr>
<tr>
<td>Dermatological</td>
<td></td>
<td>Bowen disease</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Darier disease</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Hailey–Hailey disease</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Onychomycosis</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Onychopapilloma</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Tuberosus sclerosis</td>
</tr>
<tr>
<td>Drugs</td>
<td></td>
<td>Penicillamine</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Trazodone hydrochloride</td>
</tr>
<tr>
<td>White</td>
<td>Hereditary or congenital</td>
<td>Trichothiodystrophy with PIBI(D)S</td>
</tr>
<tr>
<td>Leukonychia</td>
<td></td>
<td>Infectious</td>
</tr>
<tr>
<td>punctate</td>
<td></td>
<td>White superficial onychomycosis Acremonium spp. Aspergillus terreus Candida albicans Fusarium oxysporum Trichophyton interdigitale (mentagrophytes) Trichophyton rubrum</td>
</tr>
<tr>
<td>Dermatological</td>
<td></td>
<td>Alopecia areata</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Toxicity</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Fluorine</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Trauma</td>
</tr>
<tr>
<td>White</td>
<td>Hereditary or congenital</td>
<td>Bart–Pumphrey syndrome Basaran Yilmaz syndrome (Keratoderma, hypotrichosis, leukonychia syndrome) Bauer syndrome Blue rubber bleb nevus Heimler syndrome (partial leukonychia) Hooft disease Keratoderma with leukonychia totalis LEOPARD syndrome Leukonychia + kolonychia Leukonychia + kolonychia + deafness + knuckle pads + keratoderma palmoplantare Leukonychia + onychorrhexis + hypoparathyroidism + dental changes + cataract Leukonychia + pili torti (leukonychia subtotalis) Leukonychia + multiple sebaceous cysts + renal calculi (steatocystoma multiplex)</td>
</tr>
<tr>
<td>Nail anatomical site</td>
<td>Onychopathy</td>
<td>Associated disease</td>
</tr>
<tr>
<td>----------------------</td>
<td>-------------</td>
<td>-------------------</td>
</tr>
<tr>
<td><strong>Nail plate (cont'd)</strong></td>
<td>White (cont'd)</td>
<td>Leukonychia, axonal neuropathy, myopathic features, dilated cardiomyopathy, conduction disturbances, and arrhythmia Leukonychia, duodenal ulcer and gallstones Lowry Wood syndrome. Leukonychia totalis + epiphyseal dysplasia Vohwinkel syndrome Neurological Reflex sympathetic dystrophy Drugs Silver nitrate Sirolimus</td>
</tr>
<tr>
<td><strong>Color</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>White</td>
<td>Hereditary or congenital</td>
<td>Leukonychia striata Striated leukonychia + eruptive milia Physiological Menstruation Mountain climbers at high altitude Cardiovascular Cardiac insufficiency Myocardial infarction Gastrointestinal Hepatic Cirrhosis Wilson disease Ulcerative colitis Renal Acute rejection of renal transplants Acute renal failure Chronic renal failure Hematological Sickle cell anemia Infectious AIDS Dermatophyte infection Empyema Herpes zoster Infectious fevers (Reil's lines) Intestinal parasitic infections Leprosy Malaria Pneumonia Immunodeficiency Severe combined immunodeficiency Neoplastic Breast cancer Carcinoid Hodgkin disease Rheumatological Systemic lupus erythematosus Dermatological Alopecia areata Psoriasis Malnutrition Hypocalcemia Malnutrition Pellagra Drugs Acetazolamide Chemotherapeutic agents</td>
</tr>
<tr>
<td>Nail anatomical site</td>
<td>Onychopathy</td>
<td>Associated disease</td>
</tr>
<tr>
<td>---------------------</td>
<td>-------------</td>
<td>--------------------</td>
</tr>
<tr>
<td>Yellow</td>
<td>Hereditary or congenital</td>
<td>Aplasia cutis with dystrophic nails, Curly hair—acral keratoderma—caries syndrome, Familial amyloidosis with polyneuropathy, Incontinentia pigmenti, Macular amyloidosis with familial nail dystrophy, Pachyonychia congenita type 1 of Jadassohn–Lewandowsky, Progeria, Renal, Uremia, Hematological, Porphyria cutanea tarda, Infectious, AIDS, Dermatological, Incontinentia pigmenti, Onychomatricoma, Occupational/external environment, Nail polish, Rhus dermatitis, Drugs, Amorolfine (topical use), Amphotericin B, Carotene therapy, Dinitrochlorobenzene, Eosin, Erythromycin, Fluorescein, Gold, Lithium (distal golden yellow color), Methotrexate, Nitric acid derivatives, Oxytetracycline, Phenazopyridine, Picric acid, Tartrazine, Tetracycline, Topical corticosteroids, Toxicity, Chromium salts</td>
</tr>
<tr>
<td>Nail anatomical site</td>
<td>Onychopathy</td>
<td>Associated disease</td>
</tr>
<tr>
<td>----------------------</td>
<td>-------------</td>
<td>--------------------</td>
</tr>
<tr>
<td><strong>Nail plate (cont’d)</strong></td>
<td>Yellow (cont’d)</td>
<td>Occupational exposure: pesticides (diquat, paraquat, dinitro-orthocresol, dinobuton, dynap), epoxy system handlers (metaphenylenediamine and 4,4-methyleneedianiline), flower handlers, chromium salts (yellow ochre), dyestuffs</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Selenium intoxication</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Thallium poisoning</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Miscellaneous</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Amyloidosis</td>
</tr>
<tr>
<td><strong>Yellow nail syndrome</strong></td>
<td>Idiopathic</td>
<td>Hereditary or congenital</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Familial</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Cardiovascular</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Myocardial infarction</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Post coronary artery bypass surgery</td>
</tr>
<tr>
<td><strong>Yellow nail syndrome</strong></td>
<td>Idiopathic</td>
<td>Pulmonary</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Asthma</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Bronchiectasis</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Bronchitis</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Chronic pulmonary infections</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Chyllothorax</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Empyema</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Giant cell interstitial pneumonitis</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Pleural effusion</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Pneumonia</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Pulmonary fibrosis</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Sinusitis</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Renal</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Artificial arteriovenous fistula for hemodialysis</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Hypoplastic kidney</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Nephrotic syndrome</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Xanthogranulomatous pyelonephritis</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Endocrine</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Autoimmune hypothyroidism</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Breasts of unequal size</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Diabetes mellitus</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Thyroid disease</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Neurological</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Guillain–Barré syndrome</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Mental retardation</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Sleep apnea</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Vascular</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Arteriovenous fistula</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Raynaud phenomenon and disease</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Infectious</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Cellulitis</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Chronic pulmonary infections</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Chronic sinusitis</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Pneumonia</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Syphilis</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Tuberculosis</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Immunodeficiency</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Complete absence of IgA</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Chronic graft-versus-host reaction</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Common variable immunodeficiency</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Hypogammaglobulinemia</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Low levels of IgM</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Lymphopenia</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Macroglobulinemia</td>
</tr>
</tbody>
</table>
### Appendix

#### 925

<table>
<thead>
<tr>
<th>Nail anatomical site</th>
<th>Onychopathy</th>
<th>Associated disease</th>
</tr>
</thead>
<tbody>
<tr>
<td>Neoplastic</td>
<td></td>
<td>Anaplastic undifferentiated tumor</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Breast infiltrating ductal carcinoma</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Bronchogenic carcinoma</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Endometrial adenocarcinoma</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Gallbladder adenocarcinoma</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Hodgkin lymphoma</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Laryngeal carcinoma</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Lung adenocarcinoma</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Malignant melanoma</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Mycosis fungoides</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Sarcoma</td>
</tr>
<tr>
<td>Renal</td>
<td></td>
<td>Membranous glomerulonephritis</td>
</tr>
<tr>
<td>Rheumatological</td>
<td></td>
<td>Rheumatoid arthritis</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Systemic lupus erythematosus</td>
</tr>
<tr>
<td>Dermatological</td>
<td></td>
<td>Bullous lichen planus</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Psoriasis</td>
</tr>
<tr>
<td>Drugs</td>
<td></td>
<td>Bucillamine</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Gold</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Penicillamine</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Tiopronin</td>
</tr>
<tr>
<td>Miscellaneous</td>
<td></td>
<td>Exposure to titanium dioxide in foods, personal care items, medications, and surgical devices</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Rock hard cerumen</td>
</tr>
</tbody>
</table>

#### Shape

<table>
<thead>
<tr>
<th>Anonychia</th>
<th>Hereditary or congenital</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Abnormal or absent underlying phalanx</td>
</tr>
<tr>
<td></td>
<td>Acrogeria (Gottron syndrome)</td>
</tr>
<tr>
<td></td>
<td>AEC syndrome</td>
</tr>
<tr>
<td></td>
<td>Anonychia keratodes</td>
</tr>
<tr>
<td></td>
<td>Apical dystrophy</td>
</tr>
<tr>
<td></td>
<td>Aplastic anonychia</td>
</tr>
<tr>
<td></td>
<td>Brachydactyly with absence of middle phalanges and hypoplastic nails or brachydactyly type A5 with nail dysplasia</td>
</tr>
<tr>
<td></td>
<td>Brachymorphism–onychodusplasia–dysphalangism (BOD) syndrome</td>
</tr>
<tr>
<td></td>
<td>Coffin–Siris syndrome</td>
</tr>
<tr>
<td></td>
<td>Congenital ichthyosiform erythroderma</td>
</tr>
<tr>
<td></td>
<td>Cook syndrome</td>
</tr>
<tr>
<td></td>
<td>Cranio-fronto-nasal dysplasia</td>
</tr>
<tr>
<td></td>
<td>DOOR syndrome</td>
</tr>
<tr>
<td></td>
<td>Dyscephalic–mandibulo–oculofacial syndrome of Hallerman–Streiff–Francois</td>
</tr>
<tr>
<td></td>
<td>Ectodermal dysplasia hypohidrotic odonto-trichomelic type</td>
</tr>
<tr>
<td></td>
<td>Ectodermal dysplasia tricho-odonto-onychal type</td>
</tr>
<tr>
<td></td>
<td>Ectodermal dysplasia/skin fragility syndrome</td>
</tr>
<tr>
<td></td>
<td>Epidermolysis bullosa</td>
</tr>
<tr>
<td></td>
<td>Dowling–Meara</td>
</tr>
<tr>
<td></td>
<td>Dystrophic, acral dominant or recessive</td>
</tr>
<tr>
<td></td>
<td>Dystrophic, bullous dermolysis of the newborn</td>
</tr>
<tr>
<td></td>
<td>Dystrophic, generalized</td>
</tr>
<tr>
<td></td>
<td>Dystrophic, nails only</td>
</tr>
<tr>
<td>Nail anatomical site</td>
<td>Onychopathy</td>
</tr>
<tr>
<td>-----------------------------</td>
<td>--------------------------------</td>
</tr>
<tr>
<td>Nail plate (cont’d)</td>
<td>Anonychia (cont’d)</td>
</tr>
<tr>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
</tr>
<tr>
<td>Nail anatomical site</td>
<td>Onychopathy</td>
</tr>
<tr>
<td>---------------------</td>
<td>-------------</td>
</tr>
<tr>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
</tr>
<tr>
<td>Cardiovascular</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
</tr>
<tr>
<td>Gastrointestinal</td>
<td></td>
</tr>
<tr>
<td>Neurological</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
</tr>
<tr>
<td>Endocrine</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
</tr>
<tr>
<td>Vascular</td>
<td></td>
</tr>
<tr>
<td>Infectious</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
</tr>
<tr>
<td>Immunodeficiency</td>
<td></td>
</tr>
<tr>
<td>Neoplastic</td>
<td></td>
</tr>
<tr>
<td>Orthopedic</td>
<td></td>
</tr>
<tr>
<td>Rheumatological</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
</tr>
<tr>
<td>Dermatological</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
</tr>
<tr>
<td>Nail anatomical site</td>
<td>Onychopathy</td>
</tr>
<tr>
<td>-------------------------------------</td>
<td>------------------------------</td>
</tr>
<tr>
<td><strong>Nail plate</strong> (cont’d)</td>
<td>Beau’s line (cont’d)</td>
</tr>
<tr>
<td><strong>Shape</strong></td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
</tr>
<tr>
<td>Drugs</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
</tr>
<tr>
<td>Toxicity</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
</tr>
<tr>
<td>Trauma</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
</tr>
<tr>
<td>Miscellaneous</td>
<td></td>
</tr>
<tr>
<td>Brachyonychia and racket nail and</td>
<td></td>
</tr>
<tr>
<td>hypoplastic nails</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
</tr>
<tr>
<td>Nail anatomical site</td>
<td>Onychopathy</td>
</tr>
<tr>
<td>---------------------</td>
<td>-------------</td>
</tr>
<tr>
<td>Infectious</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
</tr>
<tr>
<td>Neoplastic</td>
<td></td>
</tr>
<tr>
<td>Rheumatological</td>
<td></td>
</tr>
<tr>
<td>Drug</td>
<td></td>
</tr>
<tr>
<td>Alcohol</td>
<td></td>
</tr>
<tr>
<td>Hydantoin</td>
<td></td>
</tr>
<tr>
<td>Phenytoin</td>
<td></td>
</tr>
<tr>
<td>Trimethadione</td>
<td></td>
</tr>
<tr>
<td>Trauma</td>
<td></td>
</tr>
<tr>
<td>Clubbing</td>
<td></td>
</tr>
<tr>
<td>Hereditary or congenital</td>
<td></td>
</tr>
<tr>
<td>Bird-headed dwarfism, Seckel syndrome type 1</td>
<td></td>
</tr>
<tr>
<td>Cartilage–hair hypoplasia, metaphyseal chondrodysplasia, McKusick type</td>
<td></td>
</tr>
<tr>
<td>Cleido-cranial dysostosis</td>
<td></td>
</tr>
<tr>
<td>Cretinism</td>
<td></td>
</tr>
<tr>
<td>Familial</td>
<td></td>
</tr>
<tr>
<td>Job syndrome (hyper-IgE syndrome)</td>
<td></td>
</tr>
<tr>
<td>Keratoderma palmoplantar and clubbing of nail</td>
<td></td>
</tr>
<tr>
<td>Nodular erythema with digital changes (Nakajo syndrome)</td>
<td></td>
</tr>
<tr>
<td>Peutz–Jeghers–Touraine syndrome</td>
<td></td>
</tr>
<tr>
<td>Physiological</td>
<td></td>
</tr>
<tr>
<td>Newborns</td>
<td></td>
</tr>
<tr>
<td>Cardiovascular</td>
<td></td>
</tr>
<tr>
<td>Congenital heart disease</td>
<td></td>
</tr>
<tr>
<td>Congestive heart failure</td>
<td></td>
</tr>
<tr>
<td>Thoracic vascular malformations</td>
<td></td>
</tr>
<tr>
<td>Venous stasis disease (toenails)</td>
<td></td>
</tr>
<tr>
<td>Pulmonary</td>
<td></td>
</tr>
<tr>
<td>Acute pneumonia</td>
<td></td>
</tr>
<tr>
<td>Ayerza syndrome</td>
<td></td>
</tr>
<tr>
<td>Nail anatomical site</td>
<td>Onychopathy</td>
</tr>
<tr>
<td>------------------------------</td>
<td>----------------------</td>
</tr>
<tr>
<td>Nail plate (cont'd)</td>
<td>Clubbing (cont'd)</td>
</tr>
<tr>
<td>Shape</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
</tr>
<tr>
<td>Gastrointestinal</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
</tr>
<tr>
<td>Esophagus</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
</tr>
<tr>
<td>Stomach</td>
<td></td>
</tr>
<tr>
<td>Small bowel</td>
<td></td>
</tr>
<tr>
<td>Small intestinal diseases</td>
<td></td>
</tr>
<tr>
<td>Colon</td>
<td></td>
</tr>
<tr>
<td>Amebiasis</td>
<td></td>
</tr>
<tr>
<td>Ascariasis</td>
<td></td>
</tr>
<tr>
<td>Bacillary dysentery</td>
<td></td>
</tr>
<tr>
<td>Carcinoma of the colon</td>
<td></td>
</tr>
<tr>
<td>Coeliac sprue</td>
<td></td>
</tr>
<tr>
<td>Crohn's disease</td>
<td></td>
</tr>
<tr>
<td>Duodenal ulcer with pyloric stenosis</td>
<td></td>
</tr>
<tr>
<td>Familial polyposis (Gardner syndrome)</td>
<td></td>
</tr>
<tr>
<td>Idiopathic steatorrhea</td>
<td></td>
</tr>
<tr>
<td>Inflammatory states of the colon</td>
<td></td>
</tr>
<tr>
<td>Laxative abuse</td>
<td></td>
</tr>
<tr>
<td>Multiple polyposis</td>
<td></td>
</tr>
<tr>
<td>Osler–Weber–Rendu disease</td>
<td></td>
</tr>
<tr>
<td>Ulcerative colitis</td>
<td></td>
</tr>
<tr>
<td>Whipworm infection</td>
<td></td>
</tr>
<tr>
<td>Hepatic</td>
<td></td>
</tr>
<tr>
<td>Active chronic hepatitis</td>
<td></td>
</tr>
<tr>
<td>Porphyria cutanea tarda</td>
<td></td>
</tr>
<tr>
<td>Primary or secondary cirrhosis</td>
<td></td>
</tr>
<tr>
<td>Secondary amyloidosis</td>
<td></td>
</tr>
<tr>
<td>Wilson disease</td>
<td></td>
</tr>
<tr>
<td>Renal</td>
<td></td>
</tr>
<tr>
<td>Chronic pyelonephritis</td>
<td></td>
</tr>
<tr>
<td>Neurological</td>
<td></td>
</tr>
<tr>
<td>Syringomyelia</td>
<td></td>
</tr>
<tr>
<td>Peripheral neuritis</td>
<td></td>
</tr>
<tr>
<td>Endocrine</td>
<td></td>
</tr>
<tr>
<td>Diamond syndrome</td>
<td></td>
</tr>
</tbody>
</table>
### Appendix

<table>
<thead>
<tr>
<th>Nail anatomical site</th>
<th>Onychopathy</th>
<th>Associated disease</th>
</tr>
</thead>
<tbody>
<tr>
<td>Myxedema</td>
<td>POEMS syndrome</td>
<td></td>
</tr>
<tr>
<td>POEMS syndrome</td>
<td>Post-thyroidectomy</td>
<td></td>
</tr>
<tr>
<td>Post-thyroidectomy</td>
<td>Seip–Lawrence syndrome</td>
<td></td>
</tr>
<tr>
<td>Thyroid cancer</td>
<td>Thyroid disease</td>
<td></td>
</tr>
<tr>
<td>Thyroid disease</td>
<td>Hematological</td>
<td></td>
</tr>
<tr>
<td>Alcohol</td>
<td>Hemoglobinopathies</td>
<td></td>
</tr>
<tr>
<td>Hemoglobinopathies</td>
<td>Methemoglobinemia</td>
<td></td>
</tr>
<tr>
<td>Methemoglobinemia</td>
<td>Polycythemia</td>
<td></td>
</tr>
<tr>
<td>Polycythemia</td>
<td>Porphyria cutanea tarda</td>
<td></td>
</tr>
<tr>
<td>Porphyria cutanea tarda</td>
<td>Primary or secondary polycythemia associated with hypoxia</td>
<td></td>
</tr>
<tr>
<td>Reduced ferritin</td>
<td>Sulfhemoglobinemia</td>
<td></td>
</tr>
<tr>
<td>Sulfhemoglobinemia</td>
<td>Vascular</td>
<td></td>
</tr>
<tr>
<td>Acrocyanosis</td>
<td>Chilblains</td>
<td></td>
</tr>
<tr>
<td>Chilblains</td>
<td>Raynaud disease</td>
<td></td>
</tr>
<tr>
<td>Raynaud disease</td>
<td>Infectious</td>
<td></td>
</tr>
<tr>
<td>Leprosy</td>
<td>Rheumatic fever</td>
<td></td>
</tr>
<tr>
<td>Rheumatic fever</td>
<td>Syphilis</td>
<td></td>
</tr>
<tr>
<td>Syphilis</td>
<td>Immunodeficiency</td>
<td></td>
</tr>
<tr>
<td>AIDS</td>
<td>Chronic familial neutropenia</td>
<td></td>
</tr>
<tr>
<td>Chronic familial neutropenia</td>
<td>Neoplastic</td>
<td></td>
</tr>
<tr>
<td>Bronchogenic carcinoma</td>
<td>Bronchopulmonary cancers</td>
<td></td>
</tr>
<tr>
<td>Bronchopulmonary cancers</td>
<td>Hodgkin disease</td>
<td></td>
</tr>
<tr>
<td>Hodgkin disease</td>
<td>Kaposi sarcoma</td>
<td></td>
</tr>
<tr>
<td>Kaposi sarcoma</td>
<td>Lymphoma</td>
<td></td>
</tr>
<tr>
<td>Lymphoma</td>
<td>Mediastinal tumors</td>
<td></td>
</tr>
<tr>
<td>Mediastinal tumors</td>
<td>Mesothelioma</td>
<td></td>
</tr>
<tr>
<td>Mesothelioma</td>
<td>Metastatic cancers</td>
<td></td>
</tr>
<tr>
<td>Metastatic cancers</td>
<td>Nasopharyngeal carcinoma</td>
<td></td>
</tr>
<tr>
<td>Nasopharyngeal carcinoma</td>
<td>Pleural tumors</td>
<td></td>
</tr>
<tr>
<td>Pleural tumors</td>
<td>Pseudotumor due to esophageal dilatation</td>
<td></td>
</tr>
<tr>
<td>Pseudotumor due to esophageal dilatation</td>
<td>Squamous cell carcinoma of the lung</td>
<td></td>
</tr>
<tr>
<td>Squamous cell carcinoma of the lung</td>
<td>Thyroid cancer</td>
<td></td>
</tr>
<tr>
<td>Thyroid cancer</td>
<td>Rheumatological</td>
<td></td>
</tr>
<tr>
<td>Rheumatological</td>
<td>Rheumatoid arthritis</td>
<td></td>
</tr>
<tr>
<td>Rheumatoid arthritis</td>
<td>Scleroderma</td>
<td></td>
</tr>
<tr>
<td>Scleroderma</td>
<td>Systemic lupus erythematosus</td>
<td></td>
</tr>
<tr>
<td>Systemic lupus erythematosus</td>
<td>Systemic sclerosis</td>
<td></td>
</tr>
<tr>
<td>Systemic sclerosis</td>
<td>Occupational</td>
<td></td>
</tr>
<tr>
<td>Occupational</td>
<td>Exposure to vinyl chloride</td>
<td></td>
</tr>
<tr>
<td>Exposure to vinyl chloride</td>
<td>Malnutrition</td>
<td></td>
</tr>
<tr>
<td>Malnutrition</td>
<td>Kwashiorkor</td>
<td></td>
</tr>
<tr>
<td>Kwashiorkor</td>
<td>Malnutrition</td>
<td></td>
</tr>
<tr>
<td>Malnutrition</td>
<td>Drugs</td>
<td></td>
</tr>
<tr>
<td>Drugs</td>
<td>Losartan, valsartan</td>
<td></td>
</tr>
<tr>
<td>Losartan, valsartan</td>
<td>Phenolphthalein</td>
<td></td>
</tr>
<tr>
<td>Phenolphthalein</td>
<td>Purgative abuse</td>
<td></td>
</tr>
<tr>
<td>Purgative abuse</td>
<td>Toxicity</td>
<td></td>
</tr>
<tr>
<td>Toxicity</td>
<td>Arsenic poisoning</td>
<td></td>
</tr>
<tr>
<td>Arsenic poisoning</td>
<td>Beryllium intoxication</td>
<td></td>
</tr>
<tr>
<td>Beryllium intoxication</td>
<td>Heroin addiction</td>
<td></td>
</tr>
<tr>
<td>Heroin addiction</td>
<td>Hypervitaminosis A</td>
<td></td>
</tr>
<tr>
<td>Hypervitaminosis A</td>
<td>Mercury poisoning</td>
<td></td>
</tr>
<tr>
<td>Mercury poisoning</td>
<td>Phosphorus poisoning</td>
<td></td>
</tr>
<tr>
<td>Phosphorus poisoning</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Nail anatomical site</td>
<td>Onychopathy</td>
<td>Associated disease</td>
</tr>
<tr>
<td>---------------------</td>
<td>-------------</td>
<td>-------------------</td>
</tr>
<tr>
<td>Nail plate (cont’d)</td>
<td>Clubbing (cont’d)</td>
<td>Trauma</td>
</tr>
<tr>
<td>Shape</td>
<td></td>
<td>Karate</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Anatomical variations</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Unilateral or limited to only several digits</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Vascular</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Aneurysm of aorta, subclavian artery, axillary or ulnar artery</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Brachial arteriovenous fistula</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Causalgia</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Dialysis fistula</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Ductus arteriosus</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Obstructed circulation</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Subluxation of shoulder</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Takayasu arteritis</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Varices of the arm</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Neurological</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Hemiplegia</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Median neuritis</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Paralysis or the brachial plexus</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Subungual perineurioma</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Syringomyelia</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Miscellaneous</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Enchondroma</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Erythromelalgia</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Felon</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Idiopathic</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Job syndrome (hyper-IgE syndrome)</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Juvenile hyaline fibromatosis II</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Local injury</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Lymphangitis</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Osteoid osteoma</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Pancoast–Tobias syndrome</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Sarcoid bone disease</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Solitary bone cyst</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Subungual epidermoid inclusions</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Tophaceous gout</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Wart of the ventral proximal nail fold</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Whitlow</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Confined to the lower extremities</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Abdominal aortic graft with sepsis</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Confined to the upper extremities</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Hashish or heroin addiction</td>
</tr>
</tbody>
</table>

**Clubbing: hypertrophic osteoarthropathy**

<table>
<thead>
<tr>
<th>Hereditary or congenital</th>
<th>Primary (Touraine–Solente–Gole syndrome)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Idiopathic</td>
</tr>
<tr>
<td></td>
<td>Familial</td>
</tr>
<tr>
<td></td>
<td>Secondary</td>
</tr>
<tr>
<td></td>
<td>Hypertrophic pulmonary osteoarthropathy</td>
</tr>
<tr>
<td></td>
<td>(Bamberger–Pierre–Marie syndrome)</td>
</tr>
<tr>
<td></td>
<td>Thoracic</td>
</tr>
<tr>
<td></td>
<td>Cardiovascular</td>
</tr>
<tr>
<td></td>
<td>Congenital heart disease</td>
</tr>
<tr>
<td></td>
<td>Congestive heart failure</td>
</tr>
<tr>
<td></td>
<td>Suppurative pulmonary lesions</td>
</tr>
<tr>
<td></td>
<td>Bronchiectasis empyema</td>
</tr>
<tr>
<td></td>
<td>Lung abscesses</td>
</tr>
<tr>
<td></td>
<td>Pulmonary aspergillosis</td>
</tr>
<tr>
<td></td>
<td>Pulmonary blastomycosis</td>
</tr>
<tr>
<td></td>
<td>Pulmonary tuberculosis</td>
</tr>
<tr>
<td>Nail anatomical site</td>
<td>Onychopathy</td>
</tr>
<tr>
<td>---------------------</td>
<td>-------------</td>
</tr>
<tr>
<td>Thoracic tumors</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
</tr>
<tr>
<td>Gastrointestinal</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
</tr>
<tr>
<td>Neurological</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
</tr>
<tr>
<td>Vascular</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
</tr>
<tr>
<td>Infectious</td>
<td></td>
</tr>
<tr>
<td>Neoplastic</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
</tr>
<tr>
<td>Anatomical variations</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
</tr>
<tr>
<td>Miscellaneous</td>
<td></td>
</tr>
</tbody>
</table>

**Dolichonychia**
- Hereditary or congenital
- Ehlers–Danlos syndrome
- Eunuchoidism
- Hypohidrotic ectodermal dysplasia
- Marfan syndrome
- Endocrine
  - Hypopituitarism

**Elkonyxis**
- Neurological
  - Reflex sympathetic dystrophy
- Infectious
  - Syphilis
- Rheumatological
  - Reiter syndrome
- Dermatological
  - Histioctysis X
- Psoriasis
- Drugs
  - Etretinate
  - Isotretinoin
  - Penicillamine
  - Retinoids
<table>
<thead>
<tr>
<th>Nail anatomical site</th>
<th>Onychopathy</th>
<th>Associated disease</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Nail plate (cont'd)</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Elkonyxis (cont'd)</td>
<td>Post trauma</td>
<td></td>
</tr>
<tr>
<td>Miscellaneous</td>
<td>Graft-versus-host disease</td>
<td></td>
</tr>
<tr>
<td><strong>Flat fingernails</strong></td>
<td>Gastrointestinal</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Hepatic</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Cirrhosis</td>
<td></td>
</tr>
<tr>
<td>Drugs</td>
<td>Polychlorinated biphenyl intoxication</td>
<td></td>
</tr>
<tr>
<td><strong>Hapalonychia</strong></td>
<td>Hereditary or congenital</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Soft nail disease</td>
<td></td>
</tr>
<tr>
<td>Neurological</td>
<td>Hemiplegia</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Peripheral neuritis</td>
<td></td>
</tr>
<tr>
<td>Endocrine</td>
<td>Myxedema</td>
<td></td>
</tr>
<tr>
<td>Vascular</td>
<td>Acrosphyxia</td>
<td></td>
</tr>
<tr>
<td>Infectious</td>
<td>Leprosy</td>
<td></td>
</tr>
<tr>
<td>Rheumatological</td>
<td>Chronic arthritis</td>
<td></td>
</tr>
<tr>
<td>Occupational</td>
<td>Occupational contact with chemicals</td>
<td></td>
</tr>
<tr>
<td>Malnutrition</td>
<td>Cachexia</td>
<td></td>
</tr>
<tr>
<td><strong>Hypoplastic nails</strong></td>
<td>Dermatological</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Lichen planus</td>
<td></td>
</tr>
<tr>
<td>Drugs</td>
<td>Alcohol</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Carbamazepine</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Hydantoin, diphenylhydantoin</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Mycophenolate mofetil</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Trimethadione</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Warfarin</td>
<td></td>
</tr>
<tr>
<td><strong>Koilonychia</strong></td>
<td>Idiopathic</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Hereditary or congenital</td>
<td></td>
</tr>
<tr>
<td></td>
<td>ADULT syndrome (acro-dermat-ungual-lacrimal-tooth syndrome)</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Bart–Pumphrey syndrome, palmoplantar keratoderma with leukonychia, deafness</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Cardio-facio-cutaneous syndrome</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Chondroectodermal dysplasia</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Congenital koilonychia associated with dome-shaped epiphyses and vertebral platyspondia</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Congenital porphyria (Günther)</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Dyskeratosis congenita</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Ectodermal dysplasia hypohidrotic and anhidrotic</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Ectodermal dysplasia pure hair-nail type</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Ellis–van Creveld syndrome</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Familial koilonychias with keratosis pilaris</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Familial koilonychias with syndematomatous cataract</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Familial severe 20-nail dystrophy</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Fissured nails, in adenoma sebaceum</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Focal dermal hypoplasia (Goltz–Gorlin syndrome)</td>
<td></td>
</tr>
<tr>
<td>Nail anatomical site</td>
<td>Onychopathy</td>
<td>Associated disease</td>
</tr>
<tr>
<td>---------------------</td>
<td>-------------</td>
<td>--------------------</td>
</tr>
<tr>
<td>Fetal exposure to polychlorinated biphenyl (PCB)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Fried tooth and nail syndrome</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Gottren syndrome (acrogeria)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Hemochromatosis</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Heredity: autosomal dominant</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Hypohidrotic ectodermal dysplasia</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Hypoplastic enamel, onycholysis, and hypohidrosis</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Idiopathic age-associated, particularly in big toes in early childhood</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Incontinentia pigmenti, Bloch–Sulzberger syndrome</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Isolated congenital dysplasia with longitudinal angular ridging</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Keratoderma palmoplantar progressiva of Meleda</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Keratoderma palmoplantar with periodontosis of Papillon–Lefever</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Kindler syndrome</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Leukonychia and sebaceous cysts</td>
<td></td>
<td></td>
</tr>
<tr>
<td>LEOPARD syndrome</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Monilethrix</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Nail–patella syndrome</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Neonatal ichthyosis–sclerosing cholangitis (NISCH)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Nezelof syndrome</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Non-familial 20-nail dystrophy</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Noonan syndrome</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Oliver–McFerlan syndrome</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Onychotrichodyplasia with neutropenia</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Palmar hyperkeratosis (Meleda type)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Porphyria cutanea tarda</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Sclerotylisis. Palmoplantar keratoderma with atrophic fibrosis of the extremities</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Steatocystoma multiplex</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Tibetans</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Tricho–odonto–onychial dysplasia</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Tricho–rhino–phalangeal syndrome</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Tricho–rhino–phalangeal syndrome II (Langer–Giedon syndrome, TRP II)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Trichoepithelioma multiplex</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Trichomegaly syndrome</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Trichooonychotic hidrotic ectodermal dysplasias</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Trichothiodystrophy</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Trichothiodystrophy with transient immunodeficiency</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Witkop syndrome or tooth and nail syndrome</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Zinsser–Engman–Cole syndrome</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Physiological</td>
<td>Aging</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Children, toenails</td>
<td></td>
</tr>
<tr>
<td></td>
<td>High altitude</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Infants</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Pregnancy</td>
<td></td>
</tr>
<tr>
<td>Cardiovascular</td>
<td>Coronary disease</td>
<td></td>
</tr>
<tr>
<td>Gastrointestinal</td>
<td>Carcinoma</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Celiac disease</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Cronkhite–Canada syndrome</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Gastrointestinal bleeding</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Helminth infection</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Inflammatory bowel disease</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Liver cell adenoma</td>
<td></td>
</tr>
<tr>
<td>Nail anatomical site</td>
<td>Onychopathy</td>
<td>Associated disease</td>
</tr>
<tr>
<td>---------------------</td>
<td>------------------------------</td>
<td>---------------------------------------------------------</td>
</tr>
<tr>
<td>Nail plate (cont’d)</td>
<td>Koilonychia (cont’d)</td>
<td>Peptic ulcer disease</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Post gastrectomy</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Renal</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Kidney transplantation</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Neurological</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Carpal tunnel syndrome</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Endocrine</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Acromegaly</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Diabetes</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Hyperthyroidism</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Hypothyroidism</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Menorrhagia</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Thyrotoxicosis</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Hematological</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Anemia</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Cystine deficiency</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Iron deficiency</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Plummer–Vinson syndrome</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Banti syndrome</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Erythropoietic porphyria</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Erythropoietin-producing tumors</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Hemochromatosis</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Hemoglobinopathy, sickle cell</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Polycythemia vera</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Porphyria cutanea tarda</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Pyruvate kinase deficiency</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Sickle cell disease</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Vascular</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Ischemia</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Peripheral arterial disease</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Raynaud phenomenon and disease</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Infectious</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Fungus</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Helminth infection</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Malaria</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Scabies</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Syphilis</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Immunodeficiency</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Severe combined immunodeficiency</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Orthopedic</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Acroosteolysis</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Rheumatological</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Rheumatoid arthritis</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Systemic lupus erythematosus</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Dermatological</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Acanthosis nigricans</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Alopecia areata</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Connective tissue disease</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Contact dermatitis, e.g. to cement, ammonium thioglycolate</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Darier disease</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Incontinentia pigmenti</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Lichen planus</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Lichen striatus</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Psoriasis</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Scleroderma</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Trachyonychia</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Occupational</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Alkalis and acids</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Chimney sweeps</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Exposure to cold water</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Hairdressers, thioglycolates</td>
</tr>
<tr>
<td>Nail anatomical site</td>
<td>Onychopathy</td>
<td>Associated disease</td>
</tr>
<tr>
<td>---------------------</td>
<td>-------------</td>
<td>--------------------</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Housewives</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Organic solvents</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Petroleum products</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Rickshaw men</td>
</tr>
<tr>
<td>Malnutrition</td>
<td></td>
<td>Avitaminosis</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Cachexia</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Pellagra</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Protein deficiency/low albumin</td>
</tr>
<tr>
<td>Drugs</td>
<td></td>
<td>Polychlorinated biphenyl intoxication</td>
</tr>
<tr>
<td>Toxicity</td>
<td></td>
<td>Alcoholism</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Maternal poisoning with polychlorinated biphenyls (PCB)</td>
</tr>
<tr>
<td>Trauma</td>
<td></td>
<td>Finger sucking</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Nail biting</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Poorly fitting shoes</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Thermal burns</td>
</tr>
<tr>
<td>Miscellaneous</td>
<td></td>
<td>Graft-versus-host disease</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Primary amyloidosis</td>
</tr>
<tr>
<td>Macronychia</td>
<td>Hereditary or congenital</td>
<td>Epidermal nevus syndrome</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Klippel–Trénaunay–Weber syndrome</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Maffucci syndrome</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Plexiform neurofibroma</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Proteus syndrome</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Tuberous sclerosis</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Von Recklinghausen disease</td>
</tr>
<tr>
<td>Neoplastic</td>
<td></td>
<td>Distant benign lipoblastomatosis in the axilla</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Fibrolipoma</td>
</tr>
<tr>
<td>Rheumatological</td>
<td></td>
<td>Connective tissue disease</td>
</tr>
<tr>
<td>Micronychia</td>
<td>Hereditary or congenital</td>
<td>Iso–Kikuchi syndrome</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Turner syndrome</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Zimmerman–Laband syndrome</td>
</tr>
<tr>
<td>Nail degloving</td>
<td>Vascular</td>
<td>Gangrene</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Dermatological</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Lichen planus</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Toxic epidermal necrolysis</td>
</tr>
<tr>
<td>Drug reactions</td>
<td></td>
<td>Miscellaneous</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Trauma</td>
</tr>
<tr>
<td>Onychauxis</td>
<td>Hereditary</td>
<td>Endocrine</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Diabetes</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Hypogonadism</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Infectious</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Leprosy</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Vascular</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Venous stasis</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Dermatological</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Pityriasis rubra pilaris</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Psoriasis</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Miscellaneous</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Trauma</td>
</tr>
<tr>
<td>Nail anatomical site</td>
<td>Onychopathy</td>
<td>Associated disease</td>
</tr>
<tr>
<td>---------------------</td>
<td>-------------</td>
<td>--------------------</td>
</tr>
<tr>
<td>Nail plate (cont’d)</td>
<td>Onychogryphosis</td>
<td>Idiopathic</td>
</tr>
<tr>
<td>Shape</td>
<td></td>
<td>Heredity and congenital</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Aplasia cutis with dystrophic nails</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Congenital malalignment of great toenails</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Curly hair–acral keratoderma–caries syndrome</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Dyskeratosis congenita</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Ectodermal dysplasia, hidrotic, Clouston syndrome</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Ectodermal dysplasia/skin fragility syndrome</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Ectodermal dysplasia with onychogryphosis</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Ectodermal malformations</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Epidermolysis bullosa</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Dowling–Meara</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Dystrophic, bullous dermolysis of the newborn</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Dystrophic, generalized</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Dystrophic, pruriginous dominant or recessive</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Dystrophic, recessive inversa</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Simplex, Ogna</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Simplex, other generalized</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Simplex, with muscular dystrophy</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Haim–Munk syndrome</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Heredity: autosomal dominant</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Iso–Kikuchi syndrome (hemionychogryphosis)</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Keratoderma palmoplantar of Thost–Unna</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Keratoderma palmoplantar progressiva of Meleda</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Keratoderma palmoplantar punctate type 1, keratoderma palmoplantaris papulosa of Buschke–Fische</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Keratoderma palmoplantar with periodontosis and onychogryphosis. Haim–Munk syndrome</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Keratoderma palmoplantar with periodontosis of Papillon–Lefevre</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Keratosis, ichthyosis, and deafness (KID syndrome)</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Olmsted syndrome</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Pachyonychia congenita with amyloidosis and hyperpigmentation</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Poikiloderma with neutropenia Clericuzio type</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Tay syndrome or IBDS (ichthyotic, brittle hair, decreased fertility, short stature) or photosensitive trichothiodystrophy</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Tricho–dento–osseous (TDO) syndrome</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Trichothiodystrophy</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Zinsser–Engman–Cole syndrome</td>
</tr>
<tr>
<td>Physiological</td>
<td></td>
<td>Aging</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Gastrointestinal</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Celiac disease</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Renal</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Uremia</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Endocrine</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Diabetes</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Hyperuricemia</td>
</tr>
<tr>
<td>Neurological</td>
<td></td>
<td>Central nervous system disease</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Peripheral nervous system disease</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Senile dementia</td>
</tr>
<tr>
<td>Vascular</td>
<td></td>
<td>Aneurysm</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Chronic digital ischemia</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Chronic venous stasis</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Elephantiasis</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Ischemia</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Peripheral vascular disease</td>
</tr>
<tr>
<td>Nail anatomical site</td>
<td>Onychopathy</td>
<td>Associated disease</td>
</tr>
<tr>
<td>---------------------</td>
<td>-------------</td>
<td>--------------------</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Thrombophlebitis</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Varicose veins</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Infectious</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Leprosy</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Lupus vulgaris</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Onychomycosis</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Syphilis</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Tuberculosis verrucosa cutis</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Variola</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Rheumatological</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Dermatomyositis</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Rheumatoid arthritis</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Systemic sclerosis</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Dermatological</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Histiocytosis X</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Ichthyosis</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Pemphigus</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Palmoplantar keratoderma, diffuse</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Psoriasis</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Pityriasis rubra pilaris</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Metabolic</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Gout</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Histidinemia</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Uricemia</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Trauma</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Foot anomalies (such as hallux valgus)</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Injury to the nail apparatus</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Trauma</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Vibrating power tools</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Miscellaneous</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Amyloidosis</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Follicular mucinosis</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Graft-versus-host disease</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Homelessness</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Sarcoid</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Onychomadesis</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Idiopathic</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Hereditary or congenital</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Amelogenesis imperfecta</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Autosomal dominant</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Congenital ingrown toenails</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Dyskeratosis congenita</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Epidermolysis bullosa</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Dowling–Meara</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Junctional, late onset</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Simplex, lethal acantholytic</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Simplex, localized</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Simplex, other generalized</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Simplex, with muscular dystrophy</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Hidrotic ectodermal dysplasia</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Idiopathic familial onychomadesis</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Keratinosis punctata</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Zinsser–Engman–Cole syndrome</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Physiological</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Childbirth</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Prolonged exposure to cold</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Gastrointestinal</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Cronkhite–Canada syndrome</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Renal</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Peritoneal dialysis</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Vascular</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Ischemia</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Peripheral arterial disease</td>
</tr>
<tr>
<td>Nail anatomical site</td>
<td>Onychopathy</td>
<td>Associated disease</td>
</tr>
<tr>
<td>----------------------</td>
<td>-------------</td>
<td>-------------------</td>
</tr>
<tr>
<td>Nail plate (cont’d)</td>
<td>Onychomadesis (cont’d)</td>
<td>Infectious</td>
</tr>
<tr>
<td>Shape</td>
<td></td>
<td>Candida albicans</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Chikungunya</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Coxsackievirus</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Fusarium solani</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Hand–foot–mouth disease</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Scarlet fever</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Syphilis</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Trichophyton tonsurans</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Typhoid</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Varicella</td>
</tr>
<tr>
<td>Orthopedic</td>
<td></td>
<td>Acroosteolysis</td>
</tr>
<tr>
<td>Neurological</td>
<td></td>
<td>Guillain–Barré syndrome</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Meningitis</td>
</tr>
<tr>
<td>Rheumatological</td>
<td></td>
<td>Dermatomyositis</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Immunodeficiency</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Kawasaki disease</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Systemic lupus erythematosus</td>
</tr>
<tr>
<td>Dermatological</td>
<td></td>
<td>Acute paronychia</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Alopecia areata</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Bullous dermatosis</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Contact dermatitis, e.g. to acrylates</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Eczema</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Erythema multiforme</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Erythroderma</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Histiocytosis X</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Lichen planus</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Morphea</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Mycosis fungoides</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Palmoplantar keratoderma, diffuse</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Pemphigoid</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Pemphigus</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Porokeratosis of Mibelli</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Psoriasis</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Stevens–Johnson syndrome</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Toxic epidermal necrolysis</td>
</tr>
<tr>
<td>Malnutrition</td>
<td></td>
<td>Acrodermatitis enteropathica</td>
</tr>
<tr>
<td>Drug reactions</td>
<td></td>
<td>Azithromycin</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Capecitabine</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Carbamazepine</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Cefaloridine</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Chemotherapeutic agents</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Bleomycin</td>
</tr>
<tr>
<td></td>
<td></td>
<td>5-Bromodeoxyuridine and radiation</td>
</tr>
<tr>
<td></td>
<td></td>
<td>5-Fluorouracil</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Methotrexate</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Mercaptopurine</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Mitotane</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Cloxacillin</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Drug-induced erythroderma</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Epidermal growth factor receptor inhibitors</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Gold</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Intracarotid 5-bromodeoxyuridine radiosensitization and radiotherapy</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Intralesional bleomycin</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Lithium</td>
</tr>
<tr>
<td>Nail anatomical site</td>
<td>Onychopathy</td>
<td>Associated disease</td>
</tr>
<tr>
<td>---------------------</td>
<td>-------------</td>
<td>--------------------</td>
</tr>
<tr>
<td></td>
<td>Onychorrhexis</td>
<td>Hereditary or congenital</td>
</tr>
<tr>
<td></td>
<td></td>
<td>ANOTHER syndrome</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Aplasia cutis with dystrophic nails</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Congenital hypoparathyroidism</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Dermatopathia pigmentosa reticularis</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Dyskeratosis congenita</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Ectodermal dysplasia, alopecia, onychodysplasia, hypohidrosis, keratoderma, abnormal teeth and deafness</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Ectodermal dysplasia, hidrotic (Clouston syndrome)</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Ectodermal dysplasia pure hair–nail type</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Familial</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Familial 20–nail dystrophy</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Homocystinuria</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Huriez syndrome or scleroatrophic and keratotic dermatosis of limbs</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Hyper- and hypopigmentation with dystrophic nails</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Nail–patella syndrome</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Onychotrichodysplasia with neutropenia</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Sclerodystrophy, Palmarplantar keratoderma with atrophic fibrosis of the extremities</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Witkop syndrome or tooth and nail syndrome</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Zinsser–Engman–Cole syndrome</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Physiological</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Aging</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Gastrointestinal</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Hepatic</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Cirrhosis</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Renal</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Hemodialysis</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Renal transplantation</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Endocrine</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Hypoparathyroidism (hypocalcemia)</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Hypothyroidism</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Hematological</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Iron-deficiency anemia</td>
</tr>
<tr>
<td>Nail anatomical site</td>
<td>Onychopathy</td>
<td>Associated disease</td>
</tr>
<tr>
<td>------------------------------</td>
<td>-----------------------</td>
<td>---------------------------------------------------------</td>
</tr>
<tr>
<td>Nail plate (cont’d)</td>
<td>Onychorrhexis (cont’d)</td>
<td>Vascular</td>
</tr>
<tr>
<td>Shape</td>
<td></td>
<td>Ischemia</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Peripheral arterial disease</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Raynaud phenomenon and disease</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Infectious</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Leprosy</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Mycotic disease</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Immunodeficiency</td>
</tr>
<tr>
<td></td>
<td></td>
<td>AIDS</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Severe combined immunodeficiency</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Rheumatological</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Osteoarthritis</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Periarteritis nodosa</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Rheumatoid arthritis</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Systemic lupus erythematosus</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Systemic sclerosis</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Dermatological</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Acrokeratoelastoidosis</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Cicatricial pemphigoid</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Darier disease</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Discoid lupus erythematosus</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Eczema</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Histioctyosis X</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Keratitis lichenoides chronica</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Leprosy</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Lichen nitidus</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Lichen planus</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Linear porokeratosis</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Multicentric reticulohistiocytosis</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Pemphigus foliaceus</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Pityriasis rubra pilaris</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Porokeratosis of Mibelli</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Reiter syndrome</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Verrucous epidermal nevi</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Metabolic</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Gout</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Malnutritional</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Acrodermatitis enteropathica</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Malnutrition</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Zinc deficiency</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Drugs</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Dimercaptosuccinic acid (DMSA)</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Electron beam therapy</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Epidermal growth factor receptor inhibitors</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Etanercept</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Itraconazole (longitudinal beading)</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Lithium carbonate</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Mepacrine (quinacrine)</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Occupational radiotherapy</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Penicillamine</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Retinoids</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Sirolimus</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Zidovudine</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Toxicity</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Fluorine</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Mercury intoxication</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Poisoning (especially arsenic)</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Polychlorinated biphenyl intoxication</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Thallium intoxication</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Trauma</td>
</tr>
<tr>
<td>Nail anatomical site</td>
<td>Onychopathy</td>
<td>Associated disease</td>
</tr>
<tr>
<td>------------------------------</td>
<td>-----------------</td>
<td>--------------------</td>
</tr>
<tr>
<td>Onychoschizia</td>
<td>Idiopathic</td>
<td>miscellaneous</td>
</tr>
<tr>
<td></td>
<td>Hereditary or congenital</td>
<td>follicular mucinosis</td>
</tr>
<tr>
<td></td>
<td>Acromegaly</td>
<td>Chondrodysplasia punctata type 2 Conradi–Hünermann–Happle</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Dento-oculocutaneous syndrome (Ackerman syndrome)</td>
</tr>
<tr>
<td></td>
<td>Dermatopathy pigmentosa reticularis</td>
<td>Histidinemia</td>
</tr>
<tr>
<td></td>
<td>Huriez syndrome or scleratrophic and keratotic dermatosis of limbs</td>
<td>Trichothiodystrophy with PIBI(D)S</td>
</tr>
<tr>
<td></td>
<td>X-linked dominant chondrodysplasia punctata</td>
<td>Renal</td>
</tr>
<tr>
<td></td>
<td>Renal transplantation</td>
<td>Hematological</td>
</tr>
<tr>
<td></td>
<td>Anemia</td>
<td>Polycythemia vera</td>
</tr>
<tr>
<td></td>
<td>Polychromatotic myeloma</td>
<td>Vascular</td>
</tr>
<tr>
<td></td>
<td>Ischemia</td>
<td>Vascular compromise</td>
</tr>
<tr>
<td></td>
<td>Porphyria cutanea tarda</td>
<td>Infectious</td>
</tr>
<tr>
<td></td>
<td>Volkmann syndrome</td>
<td>HIV</td>
</tr>
<tr>
<td></td>
<td>Systemic sclerosis</td>
<td>Infectious disease</td>
</tr>
<tr>
<td></td>
<td>Dermatological</td>
<td>Neoplastic</td>
</tr>
<tr>
<td></td>
<td>Curved nail of the fourth toe</td>
<td>Rheumatological preventative</td>
</tr>
<tr>
<td></td>
<td>Secondary to finger pulp atrophy</td>
<td>Periarteritis nodosa</td>
</tr>
<tr>
<td></td>
<td>Malnutrition</td>
<td>Occupational/external environment</td>
</tr>
<tr>
<td></td>
<td>Vitamin A deficiency (eggshell nails)</td>
<td>Frequent wetting and drying</td>
</tr>
<tr>
<td></td>
<td>Toxicity</td>
<td>Occupational</td>
</tr>
<tr>
<td></td>
<td>Crack cocaine drug abuse</td>
<td>Tea picking</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Use of detergents and chemicals</td>
</tr>
<tr>
<td>Parrot beak deformity</td>
<td>Idiopathic</td>
<td>miscellaneous</td>
</tr>
<tr>
<td></td>
<td>Hematological</td>
<td>Amyloidosis</td>
</tr>
<tr>
<td></td>
<td>Ischemia</td>
<td>Sarcoid</td>
</tr>
<tr>
<td></td>
<td>Porphyria cutanea tarda</td>
<td>Systemic sclerosis</td>
</tr>
<tr>
<td></td>
<td>Volkmann syndrome</td>
<td>Dermatological</td>
</tr>
<tr>
<td></td>
<td>Systemic sclerosis</td>
<td>Curved nail of the fourth toe</td>
</tr>
<tr>
<td></td>
<td>Secondary to finger pulp atrophy</td>
<td>Malnutrition</td>
</tr>
<tr>
<td></td>
<td>Vitamin A deficiency (eggshell nails)</td>
<td>Toxicity</td>
</tr>
<tr>
<td></td>
<td>Crack cocaine drug abuse</td>
<td>Miscellaneous</td>
</tr>
<tr>
<td>Nail anatomical site</td>
<td>Onychopathy</td>
<td>Associated disease</td>
</tr>
<tr>
<td>---------------------</td>
<td>-------------</td>
<td>--------------------</td>
</tr>
<tr>
<td><strong>Nail plate</strong> (cont’d)</td>
<td><strong>Parrot beak deformity (cont’d)</strong></td>
<td>Trauma</td>
</tr>
<tr>
<td><strong>Shape</strong></td>
<td></td>
<td>Fingertip injury</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Pincer nails</strong></td>
<td></td>
<td>Hereditary or congenital</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Epidermolysis bullosa</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Dowling–Meara</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Simplex, with muscular dystrophy</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Physiological</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Aging</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Renal</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Hemodialysis</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Infectious</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Tinea unguium</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Neoplastic</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Gastrointestinal malignancy</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Metastatic adenocarcinoma of the sigmoid colon</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Orthopedic</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Acroosteolysis</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Myxoid pseudocyst</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Subungual exostosis</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Rheumatological</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Kawasaki disease</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Osteoarthritis</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Systemic lupus erythematosus</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Dermatological</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Epidermoid cyst</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Pseudo-Kaposi sarcoma</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Psoriasis</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Occupational/external environment</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Poorly fitting shoes</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Post surgery</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Drugs</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Beta blockers</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Pamidronic acid</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Polychlorinated biphenyl intoxication</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Trauma</td>
</tr>
<tr>
<td><strong>Pitting</strong></td>
<td>Hereditary or congenital</td>
<td>Acroosteolysis with osteoporosis, Hajdu–Cheney syndrome</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Ectrodactyly – clefting (EEC1) syndrome</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Ectrodactyly – clefting (EEC3) syndrome</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Ectodermal dysplasia, hidrotic, Clouston syndrome</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Keratoderma palmoplantar with periodontosis of Papillon–Lefevre</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Osteopoikilosis: Buschke–Ollendorf syndrome</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Severe combined immunodeficiency</td>
</tr>
<tr>
<td></td>
<td></td>
<td>T-cell immunodeficiency, congenital alopecia and nail dystrophy</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Wiskott–Aldrich syndrome</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Infectious</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Fungus</td>
</tr>
<tr>
<td></td>
<td></td>
<td><em>Trichophyton soudanense</em></td>
</tr>
<tr>
<td></td>
<td></td>
<td><em>Trichophyton violaceum</em></td>
</tr>
<tr>
<td></td>
<td></td>
<td>Syphilis</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Orthopedic</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Acroosteolysis</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Rheumatological</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Dermatomyositis</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Reiter syndrome</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Rheumatoid arthritis</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Systemic lupus erythematosus</td>
</tr>
<tr>
<td>Nail anatomical site</td>
<td>Onychopathy</td>
<td>Associated disease</td>
</tr>
<tr>
<td>---------------------</td>
<td>------------------------------</td>
<td>-------------------------------------------------------------------------------------</td>
</tr>
<tr>
<td>Dermatological</td>
<td>Alopecia areata</td>
<td>Contact dermatitis, e.g. to bryozoan invertebrates (&quot;moss animals&quot;)</td>
</tr>
<tr>
<td></td>
<td>Eczematous dermatitis</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Histiocytosis X</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Lichen nitidus</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Lichen planus</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Palmoplantar keratoderma, punctate</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Parakeratosis pustulosa</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Pemphigus</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Pityriasis rosea</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Pityriasis rubra pilaris</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Psoriasis</td>
<td></td>
</tr>
<tr>
<td>Drugs</td>
<td>Ciclosporin</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Epidermal growth factor receptor inhibitors</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Fluorine</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Mepacrine (quinacrine)</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Propranolol</td>
<td></td>
</tr>
<tr>
<td>Trauma</td>
<td>Miscellaneous</td>
<td>Graft-versus-host disease</td>
</tr>
<tr>
<td></td>
<td>Sarcoaid</td>
<td></td>
</tr>
<tr>
<td>Pseudo-clubbing</td>
<td>Hereditary or congenital</td>
<td>Ectodermal dysplasia with abnormal papillar ridging or Basan syndrome</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Pyknodysostosis</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Sclerothylosis. Palmoplantar keratoderma with atrophic fibrosis of the extremities</td>
</tr>
<tr>
<td>Renal</td>
<td>Hemodialysis</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Renal failure</td>
<td></td>
</tr>
<tr>
<td>Endocrine</td>
<td>Hyperparathyroidism</td>
<td></td>
</tr>
<tr>
<td>Neoplastic</td>
<td>Metastasis</td>
<td></td>
</tr>
<tr>
<td>Toxicity</td>
<td>Exposure to excessive levels of vinyl chloride</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Radiodermatitis (chronic)</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Vinyl chloride monomer exposure</td>
<td></td>
</tr>
<tr>
<td>Shell nail</td>
<td>Pulmonary</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Bronchiectasis</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Miscellaneous</td>
<td>Sarcoaid</td>
</tr>
<tr>
<td>Thin, brittle nails</td>
<td>Idiopathic</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Hereditary or congenital</td>
<td>Acromegaly</td>
</tr>
<tr>
<td></td>
<td></td>
<td>ANOTHER syndrome</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Atrichia with nail dystrophy</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Cerebral gigantism (Sotos syndrome)</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Chondroectodermal dysplasia</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Congenital insensitivity to pain</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Costello syndrome</td>
</tr>
<tr>
<td></td>
<td></td>
<td>DOOR syndrome</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Dyskeratosis congenita</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Ectrodactyly – clefting (EEC1) syndrome</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Ectrodactyly – clefting (EEC3) syndrome</td>
</tr>
<tr>
<td>Nail anatomical site</td>
<td>Onychopathy</td>
<td>Associated disease</td>
</tr>
<tr>
<td>---------------------</td>
<td>-------------</td>
<td>--------------------</td>
</tr>
<tr>
<td><strong>Nail plate</strong> (cont’d)</td>
<td>Thin, brittle nails (cont’d)</td>
<td>Ectodermal dysplasia pure hair–nail type, Ellis–van Creveld syndrome, Epidermolysis bullosa, Junctional, with pyloric atresia, Finlay–Marks syndrome, scalp–ear–nipple syndrome, Fried tooth and nail syndrome, Homocystinuria, Hyper- and hypopigmentation with dystrophic nails, Nail–patella syndrome, Nail, tooth, ear syndrome, Oculo-tricho-dysplasia (OTD) syndrome, Odontomicrovascular dysplasia, Odontoonychodysplasia with alopecia, Popliteal pterygium syndrome (Klein syndrome), Progeria, Hutchinson–Gilford syndrome, Schöpf–Schulz–Passarge syndrome, Palmoplantar keratoderma with cystic eyelids, hypodontia, and hypotrichosis, Tricho-dento-osseous (TDO) syndrome, Tricho-occulo-dermal vertebral syndrome (arthrogryposis and ectodermal dysplasia), Tay syndrome or IBDS (ichthyotic, brittle hair, decreased fertility, short stature) or photosensitive trichothiodystrophy, Trichothiodystrophy non-photosensitive (TTDN1), Trichothiodystrophy with transient immunodeficiency, Williams elfin facies syndrome, Williams–Beuren syndrome, Zinsser–Engman–Cole syndrome.</td>
</tr>
<tr>
<td><strong>Shape</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Physiological</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Pregnancy</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Gastrointestinal</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Celiac disease</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Hemochromatosis</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Steatorrhea</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Neurological</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Reflex sympathetic dystrophy</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Spinal injury</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Endocrine</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Glucagonoma syndrome</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Hypocalcemia</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Parathyroid disease</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Thyroid disease</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Hematological</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Anemia</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Blood disorders</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Vascular</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Acrocyanosis</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Peripheral arterial disease</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Raynaud phenomenon and disease</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Infectious</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Syphilis</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Immunodeficiency</td>
<td></td>
<td></td>
</tr>
<tr>
<td>AIDS</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Orthopaedic</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Osteomalacia</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Osteoporosis</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Rheumatological</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Discoid lupus erythematosus</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Nail anatomical site</td>
<td>Onychopathy</td>
<td>Associated disease</td>
</tr>
<tr>
<td>---------------------</td>
<td>-------------</td>
<td>-------------------</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Periarteritis nodosa</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Rheumatoid arthritis</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Systemic lupus erythematosus</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Systemic sclerosis</td>
</tr>
<tr>
<td>Dermatological</td>
<td></td>
<td>Alopecia areata</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Darier disease</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Eczema</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Lichen planus</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Psoriasis (rare)</td>
</tr>
<tr>
<td>Occupational/external environment</td>
<td></td>
<td>Frequent wetting and drying</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Occupational</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Use of detergents and chemicals</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Vibrating power tools</td>
</tr>
<tr>
<td>Metabolic</td>
<td></td>
<td>Gout</td>
</tr>
<tr>
<td>Malnutrition</td>
<td></td>
<td>Acrodermatitis enteropathica</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Anorexia nervosa</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Cachexia</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Iron deficiency</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Selenium deficiency</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Vitamin A, C, or B6 deficiency</td>
</tr>
<tr>
<td>Drugs</td>
<td></td>
<td>Buspirone</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Emetine</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Epidermal growth factor receptor inhibitors</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Etanercept</td>
</tr>
<tr>
<td></td>
<td></td>
<td>5-Fluorouracil</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Gold</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Hydroxyurea</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Mitoxantrone</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Peloprenoic acid derivatives</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Topical corticosteroids</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Retinoids</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Sirolimus</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Vitamin A</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Voriconazole</td>
</tr>
<tr>
<td>Toxicity</td>
<td></td>
<td>Arsenic intoxication</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Fluorine</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Maternal poisoning with polychlorinated biphenyls (PCB)</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Mercury intoxication</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Polychlorinated biphenyl intoxication</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Radiation exposure</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Selenium intoxication</td>
</tr>
<tr>
<td>Miscellaneous</td>
<td></td>
<td>Acanthosis nigricans</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Acrokeratosis paraneoplastic of Bazex</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Amyloidosis</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Graft-versus-host disease</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Multicentric reticulohistiocytosis</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Sarcoidosis</td>
</tr>
<tr>
<td>Trachyonychia</td>
<td></td>
<td>Idiopathic</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Hereditary or congenital</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Balanced translocation 46, XX, t</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Dark red lunulae and knuckle pads</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Down syndrome</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Ectodermal dysplasia</td>
</tr>
</tbody>
</table>
### Nail anatomical site

<table>
<thead>
<tr>
<th>Onychopathy</th>
<th>Associated disease</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Nail plate (cont’d)</strong></td>
<td>Familial 20-nail dystrophy</td>
</tr>
<tr>
<td><strong>Shape</strong></td>
<td>Hereditary punctate palmoplantar</td>
</tr>
<tr>
<td></td>
<td>keratoderma</td>
</tr>
<tr>
<td></td>
<td>Immunoglobulin A deficiency</td>
</tr>
<tr>
<td></td>
<td>Selective IgA deficiency</td>
</tr>
<tr>
<td></td>
<td>Pulmonary sarcoïdosis</td>
</tr>
<tr>
<td></td>
<td>Neurological</td>
</tr>
<tr>
<td></td>
<td>Reflex sympathetic dystrophy</td>
</tr>
<tr>
<td></td>
<td>Vascular</td>
</tr>
<tr>
<td></td>
<td>Acrocyanosis</td>
</tr>
<tr>
<td></td>
<td>Hematological</td>
</tr>
<tr>
<td></td>
<td>Autoimmune hemolytic anemia</td>
</tr>
<tr>
<td></td>
<td>Immune thrombocytopenia purpura</td>
</tr>
<tr>
<td></td>
<td>Dermatological</td>
</tr>
<tr>
<td></td>
<td>Alopecia areata</td>
</tr>
<tr>
<td></td>
<td>Atopic dermatitis</td>
</tr>
<tr>
<td></td>
<td>Congenital cutaneous candidiasis</td>
</tr>
<tr>
<td></td>
<td>Darier disease</td>
</tr>
<tr>
<td></td>
<td>Dermatomyositis</td>
</tr>
<tr>
<td></td>
<td>Hay–Wells syndrome</td>
</tr>
<tr>
<td></td>
<td>Ichthyosis vulgaris</td>
</tr>
<tr>
<td></td>
<td>Incontinentia pigmenti</td>
</tr>
<tr>
<td></td>
<td>Lichen planus</td>
</tr>
<tr>
<td></td>
<td>Pemphigus vulgaris</td>
</tr>
<tr>
<td></td>
<td>Psoriasis</td>
</tr>
<tr>
<td></td>
<td>Twenty-nail dystrophy</td>
</tr>
<tr>
<td></td>
<td>Vitiligo</td>
</tr>
<tr>
<td></td>
<td>Drugs</td>
</tr>
<tr>
<td></td>
<td>Epidermal growth factor receptor inhibitors</td>
</tr>
<tr>
<td></td>
<td>Lithium</td>
</tr>
<tr>
<td></td>
<td>Trauma</td>
</tr>
<tr>
<td></td>
<td>External exposure to chemicals</td>
</tr>
<tr>
<td></td>
<td>Judo</td>
</tr>
<tr>
<td></td>
<td>Miscellaneous</td>
</tr>
<tr>
<td></td>
<td>Amyloidosis</td>
</tr>
<tr>
<td></td>
<td>Graft-versus-host disease</td>
</tr>
</tbody>
</table>
Index

Note: page numbers in italics refer to figures. Page numbers in bold refer to tables or boxes.

\textit{a}
A to T advancement flap 844
ablative lasers 376
abrasive bits, electric files 657
abscesses 150–152, 153, 302
absence of nail see anonychia
absorbent dressings 888
acantholytic dyskeratotic
acanthoma 691
acantholytic epidermolysis bullosa simplex 256
acanthosis nigricans 252
benign hereditary 258
paraneoplastic 548
acaulis 83
accessory matrix 714
acetyl cysteine 44
aciclovir, herpes simplex and 392
acid burns 873
acitretin 458
Ackerman syndrome 229
acquired immune deficiency syndrome 393, 538–541
congenital 250
herpes simplex 392
onychomycoses 356, 358–359, 360
PRP-like disease 411
psoriasis 462
reactive arthritis 462
syphilis 397
acquired monodactylous longitudinal pachyonychia 695–699
acquired reactive digital fibroma 718
acquired ungual fibrokeratoma 711–714
acral angio osteoma cutis 728
acral arteriolar ectasia 338
acral cyanosis 483
acral dominant dystrophic epidermolysis bullosa 257
acral lentiginous melanoma see acrolentiginous melanoma
acral pansclerotic morphea 528, 529
acral peeling skin syndrome 256
acral pigmentation 95–96
acral pseudolymphomatous angior keratoma of children (APACHE) 728–729
acral psoriasisform hemispherical papulosis 452
acridine orange 205
acro-dermat-ungual-lacrimal-tooth (ADULT) syndrome 228
acrocephalosyndactyly type II 247
acrocephalosyndactyly type V 247
acrocyanosis 486, 487
acrodermatitis continua (Hallopeau) 307, 450–451
acrodermatitis enteropathica 252, 258, 541–542
acrodermatitis enteropathica 252, 258, 541–542
acrodynia 594
acro dysostosis 247
acrogeria 242
acrokeratol eosidosis 443
acrokeratosis paraneoplastica 546–548
acrokeratosis verruciformis of Hopf 435
acrokeratotic poikiloderma (Weary syndrome) 225, 238
acrolentiginous melanoma 131, 132, 133, 777, 778
acromelanosis progressiva 207
confocal microscopy 207
see also subungual melanoma
acromegaly 505, 506
acromel anos is progressiva 95
acroosteolysis 35, 442–443
leprosy 399
occupational 635
with osteoporosis 246
acropachy see clubbing
acropathia ulceromutilans acquisita 509, 510
acropigmentation reticularis 95–96
acropustulosis repens 451
acrenal ectodermal dysplasia syndrome 228
acrenal ocular syndrome 261
acrosclerosis 489
Acrothe ci um nigrum 88
acrylic nails see artificial nails
acrylics 622–624, 638
pre mixed gels 653–655, 656
ACTH 586, 587
actinic keratosis 700
actinic porokeratosis, disseminated superficial 260
adalimumab
Hallopeau’s acrodermatitis continua 307
psoriasis 455, 459
pustular psoriasis 452
Adams–Oliver syndrome 242
Addison disease 505, 506
adenoma, liver 315
adhesives
artificial nails 625–626
cyanoacrylates 652
ethyl-cyanoacrylate 624–625
nail repair 649
adrenal insufficiency 505, 506
adrenocorticotropic hormone 586, 587
ADULT (acro-dermat-ungual–
lacrimal–tooth) syndrome 228
AEC syndrome 228
African-Americans
longitudinal melanonychia 12, 771
subungual melanoma 772
aggressive digital papillary
adenocarcinoma 709
aging 337–348
Neapolitan nail 498
AGNUS (asymmetric gait nail unit
signs) 82, 669
Aicardi–Goutières syndrome 259
AIDS see acquired immune deficiency
syndrome
ainhum 490
amniotic constrictions band 261
air bubbles, ultrasonography 150–152
Akt (protein kinase) 7
ALA-PDT 370
Alabama, arsenic poisoning 41
Albright hereditary osteodystrophy 247
albumin, Muehrcke’s lines 94
alcohol consumption
biomarker 40
clubbing 497
malformations 250
alcohols, on nail permeability 43
altretinoin, lichen planus 424
alkali burns 873
alkaptonuria 252, 544
allergic contact dermatitis 427, 428, 429
amorolfine 582
from manicure 659–660
nail polishes 623
see also atopic dermatitis
alopecia areata 74, 436–441
trachonychia 313, 437, 438, 439
ultrasonography 142–144
alopecia mucinosa 534
α-tocopherol, yellow nail
syndrome 493
Alstroemeria dermatitis 622
aluminum 5
newborns 298
preterm infants 40, 298
aluminum chloride 86, 730, 864, 885
amelanotic melanoma 131–133, 776, 778, 779
atypical vessel pattern 124, 125, 126
lichen planus vs 422
amfetamines 41–42
aminoethyl ethanolamine, soldering
flux 627
amoxicillin 579–580
apoptosis
en bloc resection 848–850
great toe 669
hooked nail after 874–877
on nail generation 33–34
parrot beak nail after 64
partial 848
amrinone 585
amyloidosis 544–545, 546
syndromes with 224, 251, 262
analgesics, postoperative 887–888
anatomy 1–3, 12–26, 826–827
comparative 26–32
measurements 783
children 298
optical coherence tomography 169
ultrasonography 141
anchoring knots, corneocytes 20
androgen therapy 586
anemia 94, 317, 516
aneurysmal bone cyst 725–726
angiobromas 155, 157
angiogenesis, HIV infection 538
angiogenesis multikinase
inhibitors 611
angiodysplasia circumscriptum
725
angiodysplasia corporis diffusum 543
angioleiomyoma 735–737
angiolipoleiomyoma 736
angiofibroma 252, 722
see also hemangiomas
angiooestoma 728
angiotensin II receptor blockers 585
aniline 594
anonychia 67–68, 215–227, 880, 881
differential diagnoses 925–926
grafting 880, 881, 882
hereditary 6
nail sculpturing 654
phenytoin 6
ulcerative/bullous lichen
planus 418
anorexia nervosa 515
anthrax 396
anti-CTLA-4 614
anti-endothelial cell antibodies 530
anti-PD1 614
antibiotics
for ingrowing nails 856
surgery 828, 885
wedged excision 857
anticardiolipin antibodies 525
anticoagulants 250, 585–586
anticonvulsant drugs 583
phenytoin 6, 250, 252, 575, 583
antifungal agents 581–582
boration-containing 372–373
MEI111 373
nail penetration 43–44
VT-1161 375
antimalarial agents 582–583
antiphospholipid antibodies 524
antiphospholipid antibody
syndrome 532
antiretroviral drugs 580–581
antiseptics, postoperative 888
antisynthetase syndrome 532
antithrombotics 828
antiviral drugs
antiretroviral drugs 580–581
see also virucidal agents
aortic graft infection 485
APACHE (acral pseudolymphomatous
angioxeratoma of children) 728–729
Apert–Crouzon syndrome 247
apical dysplasia of fingers 234
apical dystrophy 216
apical ectodermal ridge 6
aplasia cutis congenita see focal
dermal hypoplasia
aplasia cutis with dystrophic nails 234, 252
aplastic anonychia 67
apparent leukonychia 89, 92–94
chemotherapy 606
zinc deficiency 542
see also Terry’s nail
apremilast 455, 458
argyria 593
arrhythmia (syndrome with) 251
arsenic 41, 87, 298, 592, 593, 627–628
arsenical keratosis 700
arterial supply 22–23
  glomus cell tumor 155
ultrasonography 141
arteriovenous anastomoses 24
arteriovenous fistulae 725–726
arteriovenous malformations 724–725
arthritis mutilans 460
arthrogryposis and ectodermal dysplasia 237
artificial nails 622–623
  adhesives 625–626
  hazards 638–639
  for ingrowing nails 854–855
  premixed gels 653–655, 656
  rebalancing 653
  temporary 657
ultrasonography 153, 155
asbestos nail 440
Aspergillus niger 362
aspirin 584, 679
asthma 493
asymmetric gait nail unit signs (AGNUS) 82, 669
atenolol 584
atherosclerosis, nail bed 339
atopic dermatitis 306–307, 427
  alopecia areata vs 440
  chronic paronychia 314
  infected 303
  occupational aspects 618
  see also allergic contact dermatitis
atrichia with nail dystrophy syndrome 234
atrophy
  corticosteroids 586
  see also onchoatrophy
atypical blue nevus 783
atypical Hutchinson’s sign 120–121
atypical melanocytic hyperplasia 777–779
atypical vessel pattern
  amelanotic melanoma 124, 125, 126
dermoscopy 124, 125
aurora borealis pattern 363
autism 40
autoinflammation, lipodystrophy, and dermatosis syndrome 246
autonomic leukonychia 91
autophagia 508
avulsion 836–838
  chemical 378–379, 672
  for infections 302
  for lacerations 867
  onychomatricoma 697, 698
  for onychomycosis 379
  for traumatic dystrophies 344
  see also degloving
axial plane, MRI 177, 178
azathioprine, lichen planus 579
azithromycin 440
azoles, topical 777, 781
benoxaprofen 584
benzoyl peroxide 652
Berardinelli–Seip syndrome 503
beta-blockers 462, 584–585
betamethasone, psoriasis 456
bidet nail 66, 67, 638
BIDS syndrome see trichothiodystrophy
bifonazole 371–372
urea with 380
biochemistry 39–42
  see also histochemistry
biologics, psoriasis 455, 459–460
biomarkers 40–41
copper as 40, 298
biopsy 838–843
Bowen disease 704
confocal microscopy 206
damage from 12, 34
histology 7–12
intraoperative dermoscopy 127–128
longitudinal erythronychia 691
longitudinal melanonychia 321–322, 839–840
onycholmmal cysts 695
onychomycoses 367–368, 369
pigmented lesions 127
proximal white subungual onychomycosis 367–368
psoriasis 450
sentinel lymph node 783, 786
specimen handling 843
subungual melanoma 779, 781
biotin
  for brittle nails 87
  on nail growth 38
bird-headed dwarfism 247
bisphenol A methacrylate 653
black foot disease 592
blastomycosis 633
bleomycin, warts 679
blistering distal dactylitis 303
blisters 82
newborns 322, 323
see also bullae
Bloch–Sulzberger syndrome see
incontinentia pigmenti
blood flow
ultrasonography 141, 142
glomerus cell tumor 155, 157
lupus erythematosus 148–149
melanoma 164, 167, 168
psoriasis 146–147
vascular malformations 190
blood spots 115, 117
blood supply see arterial supply
blue digit syndrome 484
blue lunulae 498
blue nails, occupational 634
blue nevus 137, 318, 783, 784
blue rubber bleb nevus 735
blue spot 125, 126
blue toes 484
bone, removal 783
bone disorders/involvement
aneurysmal bone cyst 725–726
angioleiomyoma 736
giant cell tumors 194–195, 198,
751–752
high-resolution peripheral
quantitative CT 170–171
implantation epidermoid cysts 693
keratoacanthoma 683
metastases 770
occupational 638
on nail development 7, 20, 35,
65, 67
pincer nail 860
psoriasis 453
racket nails 884
schwannomas 741
see also osteocartilaginous tumors
bone marrow transplant,
psoriasis 455
bone morphogenetic protein (BMP)
7, 35
Börjeson–Forssman–Lehmann
syndrome 267, 268
boron-containing antifungals
372–373
Bourneville–Pringle syndrome see
tuberous sclerosis
Bowen disease 342, 701–705
confocal microscopy 206
cryosurgery 864
dermoscopy 116–117, 118, 119,
135–136
ultrasonography 164
wart vs 676
braces, for ingrowing nails 855
brachydactyly
Du Pan syndrome 247
pseudohypoparathyroidism 506
syndromes with 216, 242
type D 247, 248
brachymorphism–onychodysplasia–
dysphagism syndrome 242
brachyonychia 63, 399, 884
Brazilian pemphigus foliaceus 432
breast cancer 489
briakinumab, psoriasis 455
bridge cameras 107
brittle nail syndrome (nail fragility
syndrome) 84, 636
brittleness 42, 83
aging 339
causes listed 945–947
chemotherapy 606
grading 85
targeted anticancer therapies
610–612
treatment for 86
bronchiectasis 494
brown background, dermoscopy
115, 118
Bruton inhibitors 611, 612–613
bryozaos 626, 627
bubble boy syndrome 535
bucilamine 588
Buerger disease 485, 486
bullae
diabetes mellitus 504
hemodialysis 501
infection 302
lichen planus 418, 421, 422
see also blisters
bullous eruption of the newborn 322
bullous impetigo 302, 303
bullous pemphigoid 430–431
bullous poikiloderma (Kindler
syndrome) 225, 258
bupivacaine 832
Bureau–Barrière syndrome 509, 510
burns 872–873, 880
acrylic nail overcuring 655
hydrofluoric acid 628
Buschke–Ollendorff syndrome 263
buspirone 583
butchers
leukonychia 634
warts 632
butyl rubber gloves 639
Bywaters syndrome 531
C
C-kit genotype, melanoma 781
cactus thorn 871
cadavers, nail growth 38
cadmium 41
calcifications
angioleiomyoma 736
subungual 764–766
calculifying aponeurotic fibroma 718
calcineurin inhibitors, psoriasis 455
calcinosis, ultrasonography 148, 149
calciophylaxis 501, 502
calcipotriol, psoriasis 455, 456
calcitriol, psoriasis 456
calcium 85, 340
deficiency 542
calcium channel blockers 585
calcium gluconate, for hydrofluoric
acid burns 628, 873
calcofluor white 364
cameras 106–108
housings 109–110
cancer see chemotherapy; malignancy
Candida infections 317, 381
AIDS 539
artificial nails 638–639
chronic mucocutaneous 354,
535, 536
congenital 250
diabetes mellitus 505
diagnosis 365
distal and lateral subungual
onychomycosis 353
distribution 350
microscopy 364
occupational 632
paronychia 362
pigmentation 89
proximal subungual
onychomycosis 369
total dystrophic onychomycosis
360, 361
candy-cane nails 433
cantharidin 678–679
capillaries 23–24, 301
giant 203
hemorrhage 202, 203
SLE 523
malformations 722, 723
optical coherence
  tomography 169
capillaroscopy 201–203
acrocyanosis 486, 487
connective tissue diseases 316, 520–521, 526
diabetes mellitus 503–504
rheumatoid arthritis 532
Sjögren syndrome 530
systemic lupus erythematosus 525
systemic sclerosis 530
capillary malformations 722, 723
captopril 585
carbamazepine 250, 583
teratogenicity 575
carbidie bits, electric files 657
carbon dioxide lasers 376
ingrowing nails 857–858
carbon monoxide 592
carcinoma cuniculatum 705–707
carcinosarcoma 759
cardiac failure 483
cardiofaciocutaneous syndrome 217, 240
cardiomyopathy, syndromes with 217
carotene 587
carpal tunnel syndrome 35, 316, 510, 511
cartilage–hair hypoplasia 246
Castleman disease 518
catalyst, nail wraps 651
causalgia 512
cauterization 344
chemical 672, 856–857
cavernous hemangioma 190
CD10 dermal cells 6
cefalexin 578, 579
celiac disease 494
cellular digital fibroma 755
cement dermatitis 624
cephalosporins 578
cerebral gigantism 316, 505
cerebriform connective tissue nevus
  720–721
certolizumab pegol, psoriasis 455, 459
cervical rib, syndromes 509
chances 396–397
CHANDS syndrome 234
CHARGE syndrome 242
checkpoint inhibitors 614
Merkel cell carcinoma 738
chemical avulsion 378–379, 672
chemical burns 873
chemical cauterization 672, 856–857
chemical irritants 626–628
teratogenicity 575
see also targeted therapies
cherry hemangioma 122, 137–138
chevron nail 71, 300
chikungunya 394, 395
chilblain 487–488
chilblain lupus erythematosus 430
see also familial chilblain lupus
CHILD syndrome 242, 461–462, 767
nevus 265, 266
children 297–336
acral pseudolymphomatous
  angiolkeratomatous 728–729
congenital infantile
  fibrosarcoma 758
diabetes mellitus 503
ingrowing nails 298–299, 854
knuckle pads 719–720
melanoma 133, 318–320, 322, 781–782
nail infections 304
nevus 777
psoriasis 304–307, 445
severe combined
  immunodeficiency 535
chloramphenicol 578
chlorazol black 364
chloride
  cystic fibrosis 40
  nail plate 298
chloroprene gloves 639
chloporine 582
chlorpromazine 583
cholesterol embolism 484
cholesterol sulfate, X-linked
  ichthyosis 41
chondrodysplasia, metaphyseal, McKusick type 246
chondrodysplasia punctata
  type 1 234
chondrodysplasia punctata type 2
  (Conradi–Hünermann–Happle syndrome) 234, 267
chondrodysplasia type Grebe 242
chondroectodermal dysplasia 228
chondroid syringoma 680–681
chondromas 193–194, 195, 196, 749
see also enchondromas;
  osteochondromas
chondromyxoid fibroma 718–719
chondrosarcoma 196–198, 199, 758–759
Christ–Siemens–Touraine
  syndrome 229
chromium salts 594
chromoblastomycosis 382
chromonychia 87–96, 250
Kawasaki disease 534
occupational 633–637
psoriasis 447
systemic lupus erythematosus 524
chromosome anomalies 240
chronic mucocutaneous candidiasis
  354, 361, 381, 535, 536
chronic recurrent multifocal
  osteomyelitis 516
cicatricial pemphigoid, bullous
  pemphigoid vs 430
ciclopirox 81, 341, 370, 373, 378, 582
ciclosporin
  adverse effects 587
  lichen planus 424
  psoriasis 455, 456, 458
topical 87
cidofovir, warts 678
cimetidine, warts and 680
circumferential, curved
  fingernail 261
circumferential nails 65, 248, 249
cirrhosis 497–498
children 315
  nail minerals 40
citrullinemia 258, 542
clam-like deformity 249
claw-like fingers and toes,
  congenital 261
claw-like nail 65, 400
claws 28–32
cleaning, preoperative 828
clear cell syringofibroadenoma of
  Mascaro 682–683
cleidocranial dysostosis 246
  with micrognathia, absent thumbs, and
distal aphaingia 242
clindamycin, chronic
  paronychia 314
clippings see nail clippings
clobetasol
cryotherapy with 679–680
psoriasis 456
clofazimine 579
clopmiramine 583
clonidine 585
clorazepate 583
closures of defects 843–850
Clouston syndrome 219
clubbing 23, 59, 60, 245–246
AIDS 538
bacterial endocarditis 483
causes listed 929–933
children 299–300, 314, 315
congenital heart disease 482
Cystic fibrosis 542–543
Gastrointestinal disorders 494, 495
heroin addiction 486
implantation epidermoid cysts 182
liver disease 497
measurements 298
occupational 635
palmarplanter keratoderma and 222
paraneoplastic 546
peripheral nerve injuries 511
poisoning 633
racket nails with 63
respiratory disorders 490, 493
sarcoidosis 494
stroke 507
tuberculosis 494
see also pseudoclubbing
collodion baby 843
collodionosis 382
collodial acid, psoriasis 455
congenital onychodysplasia
of the index fingers
congenital onychodysplasia
with ichthyosiform erythroderma
and limb defects see CHILD syndrome
congenital hereditary endothelial dystrophy with nail hypoplasia 261
congenital hypertrophic lip of the hallux 141–142, 143, 327
congenital hypoparathyroidism 229
congenital ichthyosiform erythroderma 220
see also CHILD syndrome
congenital infantile fibrosarcoma 758
congenital ingrown toenails 261
congenital insensitivity to pain 258, 509
hyperhidrosis with 509
congenital leukonychia 91
congenital malalignment, great toenail 145, 325–327
congenital nevi 133–134, 318, 319, 320, 777
congenital onychodysplasia of the index fingers 24, 316–317
see also Iso–Kikuchi syndrome
congenital pigmented nevi of the nails 252
congenital porphyria ( Günther) 252, 544
congenital subungal pterygium 261
congestive heart failure, itraconazole 374–375
connective tissue diseases 520–535
children 316–317
nail fold vessels 24, 316–317, 520–521
see also collagen vascular disease
Conradi–Hünermann–Happle syndrome 234, 267
consent, photography 106, 111
consistency of nail, conditions affecting 83–87
constraints from footwear 664–667
contact dermatitis see allergic contact dermatitis; atopic dermatitis
contact lenses, manufacture 623
contagious ecthyma ( orf) 393, 394, 631–632
contraceptives, oral 586
copep, as biomarker 40, 298
copper acetate 627–628
Coral bead configuration, multicentric reticulohistiocytosis 533, 768
corneocytes 20–21, 33, 42
alopecia areata 440–441
gender 86
coronar plane, MRI 177, 178
corticosteroids
adverse effects 586–587
alopecia areata 441
atopic dermatitis 427
lichen planus 423–424
psoriasis 454–456
intralesional 457
cortisone 586
cosmetics 646–661
applications 637–638
bacterial infections 638–639
see also artificial nails; manicure
Costello syndrome 217
Index

955

cotton nail cast 854
Cowden variant, PTEN hamartoma syndrome 264, 265
coxsackie virus A6 393

crack cocaine
digital ischemia 485
parrot beak nail 64, 485, 584
cranioectodermal dysplasia 247
craniofrontonasal dysplasia 242
creatinine 498
Cremophor 608
Crohn's disease 315, 495, 496
Cronkhite–Canada syndrome 495, 496

onychomadesis 80, 496
cross-finger flap 849–850
cross-polarized photography 110
Crow–Fukase syndrome 517–518
crumbling, psoriasis 448
crush wounds 869, 870
crusted scabies see Norwegian scabies
cryoelectron microscopy 21
cryoglobulinemia 517
cryosurgery 621, 864–865
cryotherapy
clobetasol with 679–680
giant cell tumors of bone 752
mucoid pseudocyst 762
warts 679

cryptococcal whitlow 539, 540
culture, onychomycoses 364–365
curling, biopsy specimens 843
curly hair
ankyloblepharon, nail dysplasias 234
enamel hypoplasia and 231

curly hair–acrodermatitis–caries syndrome 217
curly nails 589
Curth's angle 60
curvatures
nail plate 19–20, 42
transverse overcurvature 61–62, 68
curved nail of fourth toe 64, 65, 248
Cushing syndrome 505
cutaneous calcifi es 766
cutaneous T-cell lymphoma 519, 520
cuticle (eponychium) 1, 4, 15, 30, 826
dermatomyositis 525
pterygium see dorsal pterygium removal 648
thickening 83
trauma from manicure 659

cutting force 42
cyanocrylates 638, 649, 651, 652
cystic fibrosis 542–543
chloride 40
minerals 298
ultrasonography 144, 543
cystine 85
cysts 160, 164, 167, 692
keratin cysts 182–183
onycholysis cysts 692, 694–695
satellite cysts, mucoid pseudocysts 179
see also epidermoid cysts; mucoid cysts
cytotoxic drugs see chemotherapy

d
dactylitis
infections 303
sarcoid 494
dampen dishes 652
dandelion tea 587
dapsone 579
Darier disease 92, 433–435, 583
linear 270
Darier–White disease 252
DEB–bullous dermolysis of the newborn 258
debridement 344, 378, 380
deep Koebner phenomenon 451
dep venous thrombosis 485
degloving 80, 324–325, 445
causes listed 937
lichen planus 418–419
malnutrition 541
see also avulsion; onychomadesis
demecolcylcine 578
denosumab, giant cell tumors of bone 752
dental anomalies, anonychia with 216
dental floss, ingrowing nails 854
dental spatula 829
dentists 623, 624
dentoocutaneous syndrome 229
depilatories 8, 627
depth of fi eld, photography 107
Derma-inject (Van der Velden) 679
see also Dermaject
dermatofibroma, fibrous 715–718
dermatofibrosarcoma protruberans 721, 722
dermatomyofibroma 717, 718
dermatomyositis 148, 149, 525–526
drugs causing 575
juvenile 316–317
pattern (scleroderma pattern) 317, 521, 526, 530
dermatopatlia pigmentosa reticularis 217
dermatophytoma 351, 363
dermatophytosis see onychomycoses
dermis
MRI 176, 177
ultrasonography 141
Dermojet
implantation cysts 586
local regional anesthesia 833
see also Derma-injector
dermoscopy 113–139
exostosis 746
glomer cell tumor 210
melanoma 113, 115, 116, 129, 207
follow-up 128
nail fold vessels 201, 202
nevi 777
onychomatricoma 126, 136, 137, 208, 697
onychomycoses 362–363
preoperative 827
squamous cell carcinoma 130, 209
desmoplastic melanoma 780
desquamation, Kawasaki disease 534–535
detergents 627, 628
diabetes mellitus 258, 503–505
biomarker 40–41
ingrowing nails 344
neuropathy 400
onychomycosis 340–341, 501, 505
diaphyseal aclasis see hereditary multiple exostoses; multiple cartilaginous exostosis
dibutyl phthalate 656
DICOM (standard) 111
Dieffenbachia seguine 592, 620
diet 298
digital arteries 22
digital dermoscopy, follow-up 128
digital nerves 25–26
digital photography 105–112
digital rules 111
digitocutaneous dysplasia 720
dimercaptosuccinic acid 587
N,N-dimethyl paratoluene 651
dimethyl sulfoxide 43
dimethyl urea 86
dimethyltolylamine 652
dinitro-orthocresyl 628
dinobuton 628
diode lasers 376
diphencyclopropenone 678
diphtheria, cutaneous 398
diquat 628
disability 618
disappearing digit 586
disappearing nail bed 80–81
discoid lupus erythematosus 429–430
discoloration see chromatychia
disinfection 828
dissecting ungual fibrokeratoma 712, 713
disseminated superficial actinic porokeratosis 260
distal and lateral subungual onychomycosis (DLSO) 350–355, 356, 366, 367, 369, 380, 382
dermoscopy 362–363
non-dermatophyte 381
distal digital block 833, 834
distal digital keratoacanthoma 683–686
distal embedding, ingrowing nails 854
distal groove 2
distal interphalangeal joints
mucoid pseudocysts 759, 760, 762, 763
psoriatic arthritis 460
distal nail plate avulsion 836, 837
distal subungual keratosis, localized multinucleate 689
distal wing block 833
disulfide bonds, nail plate proteins 40
dithranol 455, 457
diuretics 587
DNA, from nail specimens 41
docetaxel, onycholysis 81, 607
dogs, claw disorders 31
dolichonychia 62–63
causes listed 933
dominant dystrophic epidermolysis bullosa 254, 257
pruriginous 258
Donohue syndrome 262
DOOR syndrome 216, 234
dorsal pterygium 76–77, 826
differential diagnoses 901
lichen planus 415, 416, 417, 418
onychomatrixcomica 696
postoperative 886
treatment 877–880
double nail 874, 875
double-set punch technique, biopsy 839, 840
doxycycline 578
dressing 888
drilling
hyperkeratosis 344
nail sampling 365
for onychomycosis 380
for subungual hematoma 886
see also punching
drug abuse 41–42
drug-induced nail changes/
disorders 341, 574–604, 638
granulation tissue 729
pigmentation 135
psoriasis 461, 462
Stevens–Johnson syndrome 435
Du Pan syndrome 247
dual action nail nipper 829
duplication of nail 66
dye leaching 657, 658
dynamic optical coherence tomography (D-OCT) 169, 170
dyscephalic–mandibulooculofacial syndrome 216
dyschromatosis symmetrica hereditaria 95
dyschromia see chromatychia
dysentery 299
dysesthesia, postoperative 885
dyskeratosis congenita 85, 218, 238–239, 240, 535
dyslipoproteinemias 543
dysplasia of the fifth toenail 261
dystelephalangy (Kirner deformity) 65, 246
dystrophic epidermolysis bullosa 254, 255, 257, 258
ectoderm 6
ectodermal dysplasia(s) 227–240, 252
with abnormal papillar ridging 235
cleft lip and palate 218
cranioectodermal dysplasia 247
with distinctive facial appearance, alopecia, and polydactyly 229
Ellis–Van Creveld syndrome 228
hair–nail types 4–7, 9, 235, 236
hidrotic 238, 248
Clopton syndrome 219
trichonychotic 61
koiwonchya 61
with onychogryphosis 235
with short stature 235
skin fragility syndrome with 256
trichodontoonychial type 231
type 8 228
see also hypohidrotic ectodermal dysplasia
ectodermal dysplasia–alopecia–onychodysplasia–hypohidrosis-earlessness (AOHD) syndrome 218
ectodermal dysplasia/skin fragility syndrome 220
ectopic nails 248–249
ectrodactyly–clefting (EEC1) syndrome 219
ectrodactyly–clefting (EEC3) syndrome 219
eczema 306–307, 426–429, 428, 429
alopecia areata vs 440
education
photography for 105
salon workers 660
efaconazole 370, 371, 372
egg-shell nails 83, 400
Eikenella corrodens 304
Eisenmenger syndrome 482
elastic wire, for ingrowing nails 855
electric burrs 672
electric current 44
electric files 657
electrocautery
ingrowing nails 858
see also radiosurgery
electron microscopy 12, 20–22
elevation of the limb,
postoperative 887
elevators 828–829, 836
elonxys 75–76, 447, 589
causes listed 933–934
elliptical biopsy 839, 840
Ellis–Van Creveld syndrome 228
embryology 3–7, 214–215
embryopathies 214
emetine 580
EMLA cream 830
en bloc resection 848–850
enalapril 585
enamel hypoplasia and curly hair 231
enchondromas 193–194, 195, 746, 748–749
chondrosarcoma from 759
end-stage renal disease 315–316
endocarditis, bacterial 314, 483–484
endonyx onychomycosis 356–357
endothelial growth factor receptor inhibitors 610–612
English nail splitter 829–830
enthesitis 460
enthesopathy
psoriatic arthritis 170
enzyme detergents 628
epidermal dysplasias, anonychia 216
dermatoses with nail changes 261
epidermis, ultrasonography 141
epidermodysplasia verruciformis-like dermatoses 746
see also squamous cell carcinoma
epidermoid cysts 746
see also implantation epidermoid cysts
epidermodysplasia bullosa 250, 322, 323
degloving of nail 325
dystrophic 254, 255, 257, 258
junctional see junctional epidermodysplasia bullosa
epidermodysplasia bullosa acquisita, bullous pemphigoid vs 430
epidermodysplasia bullosa simplex 256, 323
AR BP230 deficiency 256
with hyperpigmentation 219
with scarring and hair loss 257
superficialis 256
epidermodysplasia bullosa simplex-Ogna 256
epilepsy 513
epioida see tuberous sclerosis
epinephrine 831–832
epithelial tumors 675–710
see also warts
epithelioid hemangoendothelioma 727, 728, 737–738
epithelioid hemangioma 727–728
epithelioid leiomyosarcoma 758
epithelioid sarcoma 757
epithelioma cuniculatum 705–707
eponychoium see cuticle
epoxy resin
epithelioid hemangioendothelioma
erythema
erythema elevatum diutinum 443–444, 754
erythema multiforme
erythroderma
erythema
erythema
erythrose
erythromycin
erythema
erythema
erythrosis
erythromelalgia 490
erythromycin 579
erthryrocrime 83, 94–95, 124
arteriovenous malformation 725
enlarged proximal origin 122, 123
erythropoietic protoporphyria 252
eospermatitis 626, 627
etanercept
lichen planus 424
psoriasis 455, 459
pustular psoriasis 452
ethics, photography 106
ethnic nail pigmentation 95, 96, 135
economic
longitudinal melanonychia 12, 318, 771
melanoma 772, 776, 778, 782
pigmentation 119, 135, 774
ethyl glucuronide 40
ethyl-cyanoacrylate 624–625
etretinate
adverse effects 589, 590
incontinetia pigmenti 687
lichen planus 424
paronychia 589, 591
psoriasis 458
Everest nails 72, 92, 493
everolimus 611, 612
Ewing sarcoma 759
ex vivo confocal microscopy 128, 131, 204, 205
ex vivo dermoscopy 128, 129, 130, 131
exophiin deficiency, epidermolysis bullosa simplex with 256
exostoses 260, 743–748
see also subungual exostosis
tensor digitorum tendon 826
mucoid pseudocysts and 180
preservation at surgery 848
eye drops
mydriatics 625
timolol 584, 585
eye injuries, cyanoacrylates 649
ezogabine 583

f

Fabry disease 543
facioscapulohumoral muscular dystrophy 253
familial amyloidosis with polynuropathy 251
familial benign pemphigus (Hailey–Hailey disease) 92, 432–433, 435
familial chiblain lupus 259
familial nail dysplasia 262
familial nail dystrophy, macular amyloidosis with 252, 262
familial osteochondromatosis see hereditary multiple exostoses
familial twenty-nail dystrophy 262
Fanti's variant, Hanek's procedure 861
farmyard pox 632
fat content 40
ferric chloride 856–857
fetal hydantoin syndrome 575
fetopathies 214
fibrogenin, renal failure 24
fibroblast growth factor receptor inhibitors 611, 613
fibroblastic rheumatism 534
fibrokeratoma 711–714
Bowen disease as 703
invaginated 714
onychomatricoma vs 699
periungual 161–162, 184, 185
subungual filamentous tumor vs 715
brittle nails 86
nail growth rates 38
trauma from footwear 343
general anesthesia 836
genital disease see sexually transmitted diseases
geometric pitting, alopecia areata 436, 437, 438
geometric punctate leukonychia 440
germinative matrix 1
giant capillaries 203
giant cell tumors 191–192
bone 194–195, 198, 751–752
tendon sheath 752–753
giant onychomatricoma 696
gingival fibromatosis 258
gingivitis 324, 660
Glanzmann–Riniker syndrome 535
glass fiber 620–621
glomangiosarcoma 732
glomerules bodies 24–25
MRI 177
glomerules cell tumor 137, 185–188, 189, 265, 731–735
confocal microscopy 210
dermoscopy 210
purple spot 126
ultrasonography 155, 156, 157, 186, 189
glossopalatine ankylosis syndrome 216
gloves
frozen 608
protective 638, 639
tourniquets made from 830, 831
glucagonoma syndrome 496–497
gluteraldehyde 625
glycosylated globin 40–41
glycosylation 503
gold 594
gold potassium cyanide 628
golimumab, psoriasis 455, 459
Goltz–Gorlin syndrome 219, 235
Gomori methamine silver 9
gonorrhea 392, 396
Gottron syndrome 242
Gottron's papules 317, 525
gout 543–544
graft-versus-host disease 536, 537
grafting 23, 846, 847
anonychia 880, 881, 882
for burns 880
after en bloc resection 849
melanoma 783
mucoid pseudocyst 763, 764
from nail bed 876
nail matrix 874, 875
Zook's procedure 862
granular cell tumor 741–742, 743
granulation tissue 729
granuloma annulare 443, 754
granulomas
oxalate 766
sea urchins 871–872
subungual 159, 162
see also pyogenic granuloma
granulomatosis with polyangiitis 532
grasp reflex multiple ingrown fingernails 328
Graves' disease 507, 763
gray background, dermoscopy 116–117, 119
great toe
amputation 669
congenital malalignment, transverse ridging 326–327
hallux valgus 141–142, 143, 327
dystrophy 262
exostosis under 165
onychomycosis 82
pediculosis 403
pincer nail 860
primary onycholysis 380
Pseudomonas (spp.) infections 671
secondary intention healing 849
trauma from footwear 343, 664, 665, 666, 667–668
see also ingrowing nails
Greek foot (Morton's toe) 343, 664, 665, 667–668, 669, 670
green nails
diabetes mellitus 504
occupational 629, 634
psoriasis 447
treatments 381
Greig cephalopolysyndactyly syndrome 247
Grenz rays, psoriasis 455, 458
griseofulvin, on histopathology 367
growth of nail plate 19–20, 32–34, 36–40, 73
aging 339
antifungal agents 581
chemotherapy 606
direction 34–35
diseases 38–39
measurement 36–37
physiological factors 37–38, 39
surgery 886
vascular supply on 23
yellow nail syndrome 491
Guillain–Barré syndrome, pyogenic granuloma 511
guitar playing 442, 620
gummata 398
Günther syndrome (congenital erythropoietic porphyria) 252, 544
Gupta and Gupta, positioning for photography 108, 109
gutter treatment, for ingrowing nails 855
h
habit–tic deformity 73, 514
Hailey–Hailey disease 92, 432–433, 435
Haim–Munk syndrome 70, 221
hair
hypertrichosis 38
implantation 621, 637
nails vs 27
hair and nail dysplasia 236
hairdressers 627, 634
hairy elbows syndrome 243
Hajdu–Cheney syndrome 246
half-and-half nail see uremic half-and-half nail
Hallerman–Streiff–Francois syndrome 216
hallux erectus 343, 668, 671
hallux valgus 668, 670, 672
hamartomas 264–265
eccrine angiomatous 265, 682
epidermal 92
strawberry-like 265, 266, 267
hammer toes 343, 668, 670
treatment 672
hand washing, artificial nails 638, 639
hand–foot–genital syndrome 262
hand–foot–mouth disease 393
handicap 618
Hanke's procedure 861
hang nails 83
hpalonychia 83–84
causes listed 934
Happle–Tinschert syndrome 268–269
hard keratins 15, 17, 40
hard nails 83
hard palate grafts, onycholysis 874
hardeners, nail plates 86, 650, 651
hardness see stiffness of nail
harlequin nail 494
harpoon nail 853
Hay–Wells syndrome 228
heavy metals 592–594
Heberden’s nodes 515
heel height, shoes 664
heel strike 663
Heimler syndrome type 1 250
Heimler syndrome type 2 250
Helicobacter pylori 14
Heller’s dystrophy 70
heloma 343, 666–667, 668
hemangioendothelioma
epitheloid 727, 728, 737–738
malignant 737–738
hemangiomas 722, 723
cavernous hemangioma 190
cherry hemangioma 122, 137–138
lobular capillary
hemangioma 190–191
sclerosing hemangioma 717
hematomas see subungual hematomas
hemionychogryphosis 69–70
hemiplegia 507–508
hemispherical papulosis, acral psoriasiform 452
hemochromatosis 251, 498
hemodialysis 315, 499–501, 737
hemoglobin M disease (nigremia) 253, 516
hemoglobinopathies 516
sickle cell disease 303, 516
hemorrhage
Darier disease 435
into melanoma 196
nail fold capillaries 202, 203
SLE 523
pemphigus 432
surgery 828, 885
systemic sclerosis 526
see also splinter hemorrhages; subungual hemorrhage
hemosiderin bands 87
hemostasis 828, 885
Henderson–Paterson bodies 394
Henoch–Schönlein purpura 301, 314
heparin 585
hepatic disorders see liver disease
hepatitis 497
hepatolenticular degeneration 253, 498
hepatopulmonary syndrome 497
hereditary (disorders) 213–214
see also specific disorders
hereditary anonychia 6
hereditary benign telangiectasia 253
hereditary clubbing of digits 246
hereditary hemorrhagic telangiectasia 253, 516
hereditary multiple exostoses 747–748
see also multiple cartilaginous exostosis
hereditary onychogryphosis 69
hereditary pincer nail 860
heroin 486
herpes simplex 390–392, 632
HIV infection 539, 540
herpes zoster 392, 393
herringbone nail 71, 300
HHF35 (antibody) 17
hidradenocarcinoma 709
hidrotic ectodermal dysplasias 238, 248
Clouston syndrome 219
trichoonychotic 61
high altitude 493
Everest nails 72, 92, 493
high-glycine/tyrosine proteins 40
high-resolution peripheral quantitative CT 170–171
high-sulfur proteins 40
Hildreth test 732–733
Hippocratic fingers see clubbing histidinemia 543
histiocytic processes 767
histiocytoma 716–717
histiocytosis X 536–537, 538, 767–768
histochemistry 16
interspecies homology 31
see also biochemistry; immunohistochemistry
histology 7–12, 364–369
histone deacetylases 7
history-taking, preoperative 827
HIV see acquired immune deficiency syndrome
Hjorth–Sabouraud disease 307–308
Hodgkin lymphoma 519, 520
home kits, nail polishes 623
homocystinuria 544
Hooft disease 251
hooked nail 874–877
hooves 28–32
Hope disease 251
Hopf acrokeratosis verruciformis 435
household chores 86
 housings, cameras for intraoperative photography 109–110
Howard–Dubois procedure 858
human immunodeficiency virus see acquired immune deficiency syndrome
human papillomavirus 392, 675
Bowen disease 701–702
carcinoma cuniculatum 706
Darier disease 435
type 16 16, 539, 675, 701–702
verrucous carcinoma 706
humidity, on nail permeability 43
Huntley papules 504–505
Huriez syndrome 250
Hutchinson–Gilford syndrome (progeria) 244, 252
Hutchinson's melanotic whitolw 781
Hutchinson's sign 120–121, 130, 134, 321, 773–775, 779
Mohs surgery 853
hyacinth bulbs 620
hyaline cell-rich chondroid syringoma 681
hyaline fibromatosis syndrome 248
juvenile 721, 722
hybrid-glass ionomers 624
hydantoin (phenytoin) 6, 250, 252, 575, 583
Hydrangea dermatitis 622
hydration 86
see also water content
hydrochloric acid 627–628
hydrofluoric acid 628, 629, 873
hydroquinone 587, 652
hydroxylamine 625
hydroxyurea, melanonychia striata 606
hygiene 14–15
hyper- and hypopigmentation with dystrophic nails 236
hyper-IgE syndrome (Job syndrome) 259, 535
hypereosinophilic syndrome 532
hypergranulosis, lichen planus 423
hyperhidrosis, congenital insensitivity to pain with 509
hyperkeratosis 344
focal acral 443
onychophosis 343, 344, 664, 665
trauma from footwear 343
see also subungual hyperkeratosis
hyperonychia 241–245
hyperoxiaemia 587
hyperoxaluria 542
hyperparathyroidism 506
hyperphosphatasia with mental retardation syndrome 1 262
hyperpigmentation, hypotrichosis, and dystrophy of nails 220
hyperplastic thick nails 241–245
hyperthyroidism 507
hypertrichosis 38
hypertrophic lip 665, 666, 844
congenital 141–142, 143, 327
hypertrophic osteoarthropathy 482, 497
causes listed 932–933
paraneoplastic 546
primary autosomal dominant 246
hypertrophic pulmonary osteoarthropathy 494
hypertrophy of the nail 68–70
hyperuricemia 259, 543–544
hoenalbuminemia 499
hypoalbuminemia 506
hypocalcified enamel and dystrophic nails 262
hypogonadism 505
hypohidrotic ectodermal dysplasia 227, 229
Christ–Siemens–Touraine syndrome 229
odontotrichomelic 230
hyponychial block 835
hyponychium 2, 4, 14–15, 30, 31, 827
 closures of defects 844
diseases listed 915–916
pterygium see ventral pterygium
hypoparathyroidism 505–506
congenital 229
syndrome with 251
hypoplastic nails
causes listed 934
with skeletal anomalies 241, 242
hypoplastic–enamel–onycholysis–hypohidrosis syndrome 230
hypothenar hammer syndrome 484
hypothyroidism 507
children 316
hystrix–like keratosis 220

i
IBIDS syndrome see trichothiodystrophy
ibrutinib 612–613
ibuprofen 584
ice packs 608
ichthyosis 142, 143
syndromes with 246, 250
X–linked, steroid sulfatase 41, 298
see also KID syndrome
ichthyosis follicularis–alopecia–photophobia 236
ichthyosis follicularis with alopecia 236
idiopathic atrophy of the nails 76, 419, 422, 423, 424
idiopathic familial onychomadesis 262
IFAP syndrome 236
Imamadar and Palit, positioning for photography 108, 109
imiquimod 679, 731
immersion dermography 114
ex vivo 128
immobility, on nail growth 38
immunodeficiency disorders onychomycoses 317, 356, 358–359, 360
primary 317, 535
syndromes with 237, 263
see also acquired immune deficiency syndrome
immunoglobulins, bullous pemphigoid 430–431
immunohistochemistry 15–17, 18, 33, 40
bullous pemphigoid 430
glomerulonephritis 734
keratoacanthoma 685–686
onychomatomatodesia 699
verrucous carcinoma 706
immunostaining 364
immunosuppression, therapeutic 535
immunotherapy cancer 614
warts 678
impairment 618
impetigo 302–303
implantation epidermoid cysts 182–183, 586, 692–694, 886–887
implants, ultrasonography 152–153

inclusion body fibromatosis 720–721
inclusion cysts (implantation epidermoid cysts) 182–183, 586, 692–694, 886–887
incontinentia pigmenti 83, 243, 252, 267
distal digital tumors 687
keratoacanthoma 683, 686
indigo naturalis oil, psoriasis 455, 457
infantile digital fibromatosis 720–721
infantile ingrowing nails 325–328, 854
infarcts, rheumatoid arthritis 531
infections intestinal 496
listed 390
surgery 885
see also bacterial infections; onychomycoses; viral infections
infective endocarditis 314, 483–484
inflammatory bowel disease 315, 495, 496
inflammatory linear verrucous epidermal nevus 268
infliximab psoriasis 455, 459
pustular psoriasis 452
infrared filters, photography 111
ingrowing nails 15, 20, 854
children 298–299, 854
congenital 261
conservative treatments 854
cryosurgery 865
elderly patients 344
from footwear 665
infantile 325–328, 854
isotretinoin 591
pregnancy 502
surgery 853–860
ultrasonography 145
inherited toenail dystrophy 262
initiators, acrylic nail curing 652, 665–656
inoculation synovitis 871
insoles 672
instrumentation, surgery 828–830
interferon alfa 588
interferon beta 588
interferonopathies (type 1) 259
interleukin–2, low level 538
interleukin inhibitors, psoriasis 459–460
International Society for Dermoscopy, register of congenital nevi 133
intracytoplasmic hyaline eosinophilic inclusion bodies 394
intralesional therapy
corticosteroids 457
adverse effects 586
psoriasis 457
warts 679
intraoperative confocal microscopy 783
intraoperative dermoscopy 127–128, 129, 130
intraoperative pain 885
intraoperative photography 109–110
intravascular papillary endothelial hyperplasia 726–727
invaginated fibrokeratoma 714
invulcrin 17
iontophoresis 43, 44, 377, 456
iron adverse effects 594
as biomarker 40
deficiency 85, 317, 542
koilonychia 299
nail plate 298
oral 87
ironing, for ingrowing nails 855–856
irregular pattern, parallel microlines 120
irritants, chemical 626–628
ischemia 23, 484–485
ISO, photography 107, 111
ISO–Kikuchi syndrome 66, 69–70, 243, 244, 245
isotretinoin, ingrowing nails 591
itching infections from 303
inflammatory linear verrucous epidermal nevus 268
itraconazole 370, 374–375, 581
chronic mucocutaneous candidiasis 381
yellow nail syndrome 493
ixekizumab, psoriasis 455, 460

J
Jackson and Lawler syndrome 223
Jackson–Lawler phenotype, keratins 17
Jadassohn–Lewandowsky syndrome 223
Janeway lesions 483
Japanese brocade weavers, microtrauma 619
Japanese ethnicity
longitudinal melanonychia 12, 771
melanoma 772, 782
Job syndrome 259, 535
jpeg format 110–111
judo 620
junctional epidermolysis 255
junctional epidermolysis bullosa 255, 257
with respiratory and renal involvement 257
junctional epidermolysis bullosa inversa 257
juvenile dermatomyositis 316–317
juvenile digital fibromatosis 720–721
juvenile hyaline fibromatosis syndrome 721, 722
juvenile pityriasis rubra pilaris 409–410
juvenile xanthogranuloma 443, 444, 768

K
K101 Nail Solution 373
Kabuki syndrome type 1 262
Kaposi sarcoma 539, 540, 737, 756
karate 620
Kawasaki disease 325, 534–535
Keipert syndrome 247
keloid 719, 887
fibromas vs 717
Kenny–Caffey syndrome type 2 262
keratin cysts 182–183
keratins 4–5, 15–17, 19, 21–22, 40
conditions modifying 85
interspecies homology 29, 31
lichen planus 423
radiation exposure 42
strength 42
keratitis, ichthyosis, and deafness (KID) 222–223, 250, 269
keratoacanthoma 83, 159, 161, 182
distal digital 683–686
wart vs 677
keratoderma with leukonychia totalis 221
keratosis cristaum 83
keratosis follicularis see Darier disease
keratosis lichenoides chronica 426
keratosis linearis with ichthyosis congenita and sclerosing
keratoderma 246
ketoconazole 581
KID syndrome (keratitis, ichthyosis, and deafness) 222–223, 250, 269
kidney see renal disorders
Kikuchi syndrome (Iso–Kikuchi syndrome) 66, 69–70, 243, 244, 245
Kindler syndrome 225, 258
Klirn syndrome 65, 246
Klein syndrome (popliteal pterygium syndrome) 216, 231
Klick syndrome 246
Klippel–Trénaunay syndrome 253, 723, 724
knuckle pads 185, 719–720
syndromes with 251
PLACK syndrome 225
Koebner phenomenon 451
Koener tumors 710–711
koilonychia 4, 59–61, 516
aging 338
causes listed 934–937
children 299
cold exposure 621
disorders including 251
hemochromatosis 498
occupational 637
syndromes with 248
Kosaka procedure 861
kwashiorkor 541

L
L-dopa 583
la Sagrada Familia sign, onychomatriomata 130
lacerations 867–869
fragmentation injury 866, 869
lacquer nail 67, 581, 582
lacrimo-auriculodentodigital (LADD) syndrome 230
lacunae, onychomycosis 351–352
lamellar dystrophy 301
lamellar nail splitting 74–75, 299, 300, 666
lamivudine 580
Langer–Giedion syndrome 232
Langerhans cell histiocytosis (histiocytois X) 536–537, 538, 767–768
Larsen syndrome, autosomal dominant 247
larva migrans 405
laryngoonychocutaneous syndrome 257
laser therapy
ingrowing nails 857–858
onychomycosis 375–377
psoriasis 455, 458
warts 680
lateral deviation of nail plate postoperative 886
see also malalignment of the great toenail
lateral longitudinal nail biopsy 842
lateral nail folds
 closures of defects 846
intralesional therapy, psoriasis 457
lateral rotation, fifth toe 668–669
Laugier–Hunziker lentiginoses 135
Laugier–Hunziker–Baran syndrome 495, 771, 774
adrenal insufficiency vs 505
lead 41, 594
lectin stains 368
LED (light-emitting diodes), ultraviolet radiation 656
lefunomide, psoriasis 455, 459
legal aspects, photography 111
Leiner disease 304
leiomyomas 736
fibromas vs 717
leiomyosarcomas 758
leishmaniasis 405, 630
Lempert elevator 829
lenses, photography 107
lentiginoses 135
lentiginous pattern, melanoma 780
see also acrolentiginous melanoma
lentigo 135
nail matrix 131
lentigo simplex 777
Leopard syndrome 250
leprochaunism 262
leprosy 94, 398–401, 504
Léri syndrome 247
Lesch–Nyhan syndrome 260, 544
leukemia 518–519
leukonychia 89–94, 251
AIDS 538
alopecia areata 438–440
apparent see Terry’s nail
capillary malformations with 722, 723
chemotherapy 606, 607
classification 89, 90
differential diagnoses 921–923
with koilonychia 251
leprosy 399, 400
occupational 634
optical coherence tomography 170
with peripheral nerve injuries 511
psoriasis 94, 447, 448
renal transplantation 502
syndromes with 251
zinc deficiency 542
see also transverse leukonychia
leukonychia striata 251
Kawasaki disease 534
paraneoplastic 548
leukonychia totalis 90–91, 250
with epiphysial dysplasia syndrome 251
with PPK and congenital alopecia 251
leukonychia trichophytica 355
leukonychia variegata 91, 92
levothyroxine 587
Lgr6 (Wnt signaling pathway) 368
leukonychia with epiphyseal dysplasia 846
LSD (light-emitting diodes), ultraviolet radiation 656
limb bud 6
limb–mammary syndrome 228
LIMX1B (transcription factor) 6
Lindsay’s nail see uremic half-and-half nail
linear Darier disease 270
linear porokeratotic groove 269–270
linear psoriasis 268
lipids
aging 340
disorders 543
lipoid proteinosis 543
lipoomas 192, 754, 755
liquid, acrylic nails 652
lithium 583
psoriasis 462, 583
liver disease 497–498
children 315
terbinafenine and 374
lobular capillary hemangioma 190–191
local anesthetic agents 831–832
allergic contact dermatitis 624
local regional anesthesia 830–836
for intralesional therapy 457
postoperative 887
preoperative explanation 827
localized multinucleate distal subungual keratosis 689
Locke elevator 829
long nails 648
artificial 653
longitudinal apparent leukonychia 94
longitudinal erythronychia 94, 690, 691
arteriovenous malformation 725
Bowen disease as 704
longitudinal grooves 70–71
mucoid pseudocyst 760, 761
longitudinal leukonychia 92
longitudinal melanonychia (LM) 11, 12, 770–773, 777
adrenal insufficiency 505
angiookeratoma 725
biopsy 321–322, 839–840
Bowen disease 703
children 318, 319, 320–322
fluconazole 581
interferon alfa 588
lichen planus 414, 415, 423
melanoma from 778
longitudinal melanonychia (LM) (cont’d)
onychomatricoma 696
pregnancy 502, 503
spontaneous regression 786–787
subungual seborrheic keratosis 687
suspicious features 775–777
systemic lupus erythematosus 524
ultrasonography 164
longitudinal pachyleukonychia 251
longitudinal pachyonychia, acquired monodactylous 695–699
longitudinal pigmentation, repetitive trauma-induced 135
longitudinal ridges 71, 826
aging 339, 340
lichen planus 411–412
psoriasis 447
see also melanonychia striata
longitudinal streaks
causes listed 910
onychopapilloma 690–691
longitudinal xantholeukonychia 121–122
Love’s pin test 732, 733
Lovibond’s angle 60
low-sulfur proteins 40
Lowry–Wood syndrome 251
luliconazole 371
lunula 1, 4, 12–13
absent 499
AIDS 538
aplopecia areata 438, 439
blue 498
cardiac failure 483
diseases listed 903–905
erythema 94–95
leprosy 94
lichen planus 412–413, 414
magnetic resonance imaging 176
on nail shape 35–36
psoriasis 446, 453
red see red lunula
surgery 886
see also pseudomacrolunula
lupus erythematosus
discoid 429–430
familial chilblain lupus 259
nail fold vessels 24
ultrasonography 148–149, 150
see also chilblain lupus
erythematosus; systemic lupus erythematosus
lupus erythematosus unguium mutilans 430, 524
lupus vulgaris 401
Lyell syndrome 79
lymph nodes biopsy 783
melanoma 786
lymphangiomatosis circumspectum 731
lymphangitis, herpes simplex 392
lymphatic drainage, yellow nail syndrome 491–493
lymphedema, yellow nail syndrome 491, 492, 493
lymphedema with yellow nails 260
lymphoma 519–520
APACHE vs 729
lyonization 265
m
Mabry syndrome 262
macronychia 65–66
causes listed 937
macular amyloidosis with familial nail dystrophy 252, 262
Maffucci syndrome 749, 750
chondrosarcoma from 759
magnesium, aging 340
magnetic resonance angiography
glomus cell tumor 187, 188, 189
osteoid osteoma 194
magnetic resonance imaging 175–200
chondrosarcoma 196–198, 199
exostosis 746
fibrokeratoma 712–713
fibromas 717
giant cell tumors 191–192, 198
of tendon sheath 753
glomus cell tumor 185–186, 187–188, 733
implantation epidermoid cysts 182–183, 693
keratoacanthoma 182, 683–684
melanoma 196, 199
mucoid pseudocysts 178–179, 761
onychomatricoma 183, 698
osteocartilaginous tumors 193
osteoid osteoma 194, 197, 198, 750–751
preoperative 827–828
psoriatic arthritis 460
squamous cell carcinoma 196
vascular malformations 190
venous malformations 723–724
warts 181
malalignment of the great toenail 145, 261, 325–327, 881–883
see also lateral deviation of nail plate
malaria 406
anemia 317
Malassezia (spp.) 365
malignancy 546–549
aging 341–342
dermatofibrosarcoma protuberans 721, 722
enchondromas 749
epithelial tumors 701–710
epithelioid hemangioendothelioma 727, 728
glomangiosarcoma 732
granular cell tumor 741–742, 743
leukemia 518–519
longitudinal erythromyotonia 94
onychocytic carcinoma 699
pyogenic granuloma vs 730
radiation exposure 621, 622
red lunula 519–520
renal transplantation 502
schwannoma 741
spiroadenoma 682
subungual 196–199
vascular tumors 737–738
see also lymphoma; melanoma; metastases; paraneoplastic syndromes; squamous cell carcinoma; specific tumors
malignant hemangioendothelioma 737–738
malnutrition 541
mammary–digital–nail syndrome 263
mandibuloacral dysplasia 246
with type A lipodystrophy 247
manicure 646–649
complications 622–623, 658–660
see also cosmetics
manicurists 623
education 660
Marfan syndrome, dorsal pterygium 76
matrical block 834
matrix see nail matrix
matrix biopsy 839–842
matrix cysts 693–694
matrix doubling syndrome 241
McKusick type metaphyseal chondrodysplasia 246
ME1111 (antifungal) 373
measurements
anatomy 783
children 298
nail growth 36–37
measuring scales, photography 111
mechanical forces, nail growth 19–20
mechanical onycholysis 81
median canaliform nail dystrophy 152, 154
median nail dystrophy 70, 589
median nerve block 835
medications on nail growth 39
preoperative assessment 828, 885
see also drug-induced nail changes/disorders
Meissner's lines 592, 593, 606
megalodactyly 65, 247
Meissner corpuscles 739
MEK inhibitors 610–612
melanin
fungal infections 88–89
half-and-half nail 500
melanocyte-stimulating hormone 587
melanocytes 10–12, 770
focal activation 777, 781
melanocytic hyperplasia 115, 128
atypical 777–779
benign 777, 781
melanocytic lesions 770–787
melanocytic nevi 120, 265, 777
dermoscopy 128–130
melanoma 11–12, 342, 776, 777–779
children 133, 318–320, 322, 781–782
confocal microscopy 205, 206, 207
dermoscopy 113, 115, 116, 129, 207
follow-up 128
diagnostic algorithm 775–777
Hutchinson's sign 120–121
melanonychia striata vs 130–131, 132
Mohs surgery 853
nevi vs 777
prognosis 785–786
pyogenic granuloma vs 730, 779
subungual 196, 199, 771–777
diagnostic algorithm 775–777
histopathology 779–781
prognosis 785–786
treatments 782–783
treatments 782–783
ultrasonography 164, 167, 168
see also acrolentiginous melanoma;
amelanotic melanoma;
superficial spreading melanoma
melanonychia 11–12
AIDS 538–539
chemotherapy 606
dermoscopy 205, 206
ROI 113
from footwear 665, 669
free edge 127
functional 777, 781
fungal 88–89, 363
from hormone treatment 587
hydroxyurea 606
melanoma vs 130–131, 132
hyperthyroidism 507
targeted anticancer therapies 612
ultrasonography 164
see also longitudinal melanonychia;
longitudinal ridges
Meltrex® formulation, itraconazole 370, 375
membrane-coating granules 12
Mendelian Inheritance in Man, numbers 214
mending of nails 649, 650
menstruation 502–503
Mepitel® (dressing) 888
mercury 594
allergy 422
Merkel cell carcinoma 738
Merkel cells 5, 16
mesenchyme 6
mesoderm 6
metacarpal block 835
metals 592–594
allergy 422
metamfenetamine 41–42
metaphyseal chondrodysplasia,
McKusick type 246
metastases 548–549, 768–770
granular cell tumor 742
melanoma 785–786
metastasizing pseudomelanoma 783
methacrylates 623, 651, 652
see also bisphenol A methacrylate;
methylmethacrylate
methemoglobinemia 635–637, 653
methotrexate
keratoacanthoma 686
psoriasis 455, 457, 458
methylene blue
mucoïd pseudocyst surgery 762, 764
photodynamic therapy 377
methyleneglycol 650, 651
methylmethacrylate 623, 624, 625
methylphenidate 583–584
1-methylquinoxalinium-p-toluene
sulfonate 625
meticillin-resistant Staphyloccoccus aureus 298
Mibelli, porokeratosis of 441
micro-Hutchinson's sign 120, 121, 130
micrographic surgery see Mohs surgery
microlines, parallel 117, 120
micronychia 65–66
causes listed 937
microscopic polyarteritis 533
microscopically controlled surgery see Mohs surgery
microscopy
onychomycoses 364
see also histology
microtrauma
blood spots 115
koilonychia 299
leukonychia 91, 542
nail plate thickening 447–448
neuromas 191
occupational 618–620, 636, 637
osteocondromas 193
paronychia 610
microwave radiation 621
midazolam 828
middle phalanges, syndromes with absence 242
midface retraction syndrome 263
migratory circinate epidermolysis bullosa simplex 256
Milian's lilac arch 397
milker's nODULES 632
milky-red areas 124, 125
MIM numbers 214
minocycline 578, 579
mirror sign, onychomatricoma 130
mirrorless cameras 107
mixed connective tissue disease 525–526
mixed pattern onychomycosis 361
Mohs surgery 850–853
squamous cell carcinoma 705
molecular diagnosis
melanoma 781
onychomycoses 369–370
molluscum contagiosum  394, 395
monochloroacetic acid  678
monomers, acrylic nails  652–653, 654
Morey and Burke’s nail  93
Morton’s toe  343, 664, 665, 667–668, 669, 670
mosaic disorders  264–270
motor oils  630
mottled pigmentation  epidermolysis bullosa simplex with  256
mouse, nails  30, 31
moxifloxacin  579
mTOR inhibitors  610–612
mucin, mucoid pseudocyst  760, 761, 762
mucinous syringometaplasia  677–678
mucocutaneous lymph node syndrome (Kawasaki disease)  325, 534–535
mucoid pseudocysts  178–180, 341, 342, 759–763, 764, 844
distal interphalangeal joints  759, 760, 762, 763
fissures and  181
osteoarthritis  178, 341, 759
peduncles  179, 181
mucous cysts  160, 164
Muehrcke’s bands  93–94, 499
causes listed  910
renal transplantation  501–502
zinc deficiency  542
multicentric reticulohistiocytosis  533, 768
juvenile xanthogranuloma  443, 444, 768
multiple carboxylase deficiency  535
multiple cartilaginous exostosis  260
see also hereditary multiple exostoses
multiple congenital anomalies–hypotonia–seizures syndrome  263
multiple exostosis syndrome see hereditary multiple exostoses
multiple myeloma  517–518
multiple sclerosis  513
multiple system atrophy  513
multiple puncture technique, warts  679
mumps  38
murderer’s thumb  247, 248
muscular dystrophy, epidermolysis bullosa simplex with  256
musicians  620
mutilating palmoplantar keratoderma with periorificial keratotic plaques (Olmsted syndrome)  223, 443
*Mycobacterium marinum*  392, 402, 630–631
mycosis fungoides  519, 520
mydriatics  625
Myhre syndrome  263
myiasis, subungual  404
myofibroblastic sarcoma  756
myositis ossificans  757
myxoid cysts  164, 167
occupational  619
see also mucoid pseudocysts
myxoid pleomorphic fibroma  718
myoinflammatory fibroblastic sarcoma  758
myxoma  754–755, 756

n
nab-paclitaxel  608
Naegeli–Franceschetti–Jadassohn syndrome  220
nail bed  1, 4, 13–15, 826
atherosclerosis  339
biopsy  839
closures of defects  847
Darier disease  435
“disappearing”  80–81
diseases listed  905–915
grafting from  876
hyperkeratosis see subungal hyperkeratosis
keratins  17
lichen planus  418, 423
Mohs surgery  853
mucoid pseudocysts  180
on nail growth  35
onychopapilloma  689–691
pigmentation  96
psoriasis  448–449, 454
ultrasonography  141
nail biting see onychophagia
nail brushing  14
nail care, inadequate  344
nail clippings
bacteriology  14
cirrhosis  497
fungal infections  365–366, 367
minerals, cystic fibrosis  298, 542
monitoring substance
exposure  42, 298, 575
onychomatrixica  697, 698
softening techniques  8
nail disorder non-syndromic congenital  2  251
nail fold(s)  1, 15
AIDS  539
capillary microscopy see capillaroscopy
coccal angiomatosis  731
lichen planus  411
neovascularization  203
psoriasis  446
synechia  879
systemic sclerosis  526, 527
see also lateral nail folds; proximal nail fold
nail fold vessels  23–24, 201–202
arthropathy  461
acrocyanosis  486, 487
children  301
connective tissue diseases  24, 316–317, 520–521
dermatomyositis  526
diabetes mellitus  503–504
hemorrhage  203
schizophrenia  514
systemic lupus erythematosus  24, 316, 521, 523, 525
nail fragility syndrome  84, 636
nail matrix  1, 12–13, 30, 32–34, 826
arthropathy  461
biopsy  839–842
closures of defects  847–848
distance to bone  783
grafting  874, 875
histology  10
intraoperative dermoscopy  127–128
leiomycosis  123
lichen planus  411–418
Mohs surgery  853
optical coherence tomography  169
psoriasis  446–448, 454
nail plate  1, 5, 17–22, 30, 32, 826
children  297–298
consistency  83–87
differential diagnoses  916–948
distal avulsion  836, 837
electron microscopy  20–22
hardeners  86, 650, 651
histochemistry  16
histology  7–9
lateral deviation  886
see also malalignment of the great toenail
lichen planus  415, 416
magnetic resonance imaging
176, 177
narrowing for ingrowing
nails 856–858
optical coherence
tomography 169
production 32–34
protein 40
psoriasis 447–448
removal 344
ridges 19, 71
strength 42
use in surgery 847
washboard 73, 324
see also cosmetics; nail plate under
growth
nail polishes 623, 649, 656
allergy 660
hardening nails 86
hazards of 638–639
removal 647, 649
UVA-curing 656
Nail Prep (softening agent) 8
nail shedding see onychomadesis
nail, tooth, ear syndrome 230
DOOR syndrome 216, 234
nail trichrome vitiligo 96, 445
nail wraps 650–652
nail–patella syndrome 6, 68,
216–227, 243
Ewing sarcoma 759
Nair (depilatory agent) 8
Nakajo–Nishimura syndrome 246
narcissus bulbs 620
nasodigitoacoustic syndrome 247
Nasturtium dermatitis 622
Native Americans, subungual
melanoma 772
Naxos disease 223
Neapolitan nail 94, 338, 339, 498
necrosis, complicating surgery 885
necrotizing vasculitis 525–526, 531
needle phobia 830
needles, local regional
anesthesia 832
Neisseria gonorrhoeae 392, 396
NEMO mutation 687
neodymium:yttrium–aluminum–
garnet lasers 376, 377
warts 680
neonates see newborns
Neoscytalidium dimidiatum
353–354, 357
neovascularization, nail folds 203
nephrotic syndrome 501
nerve supply 25–26, 827, 830, 832
nerve territory oriented macroductyly
(NTOM) 65
nervous system disorders 507–513
neurilemmomas (schwannomas) 158–159, 191, 740–741
neuroendocrine tumor 738
neurofibromas 191, 192, 264,
739–740
neurofibromatosis type 1
glomus cell tumor 265
nevi mimicking 784–785
Recklinghausen syndrome 260
neuromas 191, 739
confocal microscopy 210
systematized multiple
fribrillary 740
neuropathy 509
leprosy 400, 401, 504
syndromes with 222, 251
see also peripheral nerve injuries
neutron activation analysis 298
nevi 775
blue 137, 783
blue rubber bleb 735
cerebriform connective tissue
(type) 720–721
CHILD syndrome 265, 266
comparative genomic
hybridization 322
genetic 133–134, 318, 319,
320, 777
congenital pigmented 252
mimicking neurofibromatosis type 1
784–785
porokeratotic eccrine 269–270
verrucous epidermal
691–692
inflammatory linear 268
see also epidermal nevus;
melanocytic nevi
nevus sebaceous 264
newborns
blisters 322, 323
bullous eruption 322
DEB–bullous dermolysis 258
drug screening 298, 502
gangrene 325
ingrowing nails 854
koilocyphia 299
nail minerals 298
staphylococcal infections 304
teratogenic drugs 575
Veillonella infection 303–304
nickel 41
nicotine 41
nicotine nails 494
nifedipine 585
nigremia 253, 516
nimesulide, psoriasis 455
nippers 829–830
nitric acid 680
nitrile rubber gloves 639
nitrogen, newborns 298
nodular melanoma 777–778, 780
nODULES 617–637
nodule 888
non-Hodgkin lymphoma 520
non-Langerhans cell
histiocytoses 768
see also juvenile xanthogranuloma
non-melanoma Hutchinson's
sign 774–775
non-vasculitic neutrophilic
dermatosis 541
nonoxynol-6 625
Noonan syndrome 240
Nora's lesion 747
Norwegian scabies 402–403
HIV infection 539
leukemia 519
notches 877–879, 880
Darier disease 433
nucleoside/nucleotide reverse
transcriptase inhibitors
580–581
nutritional disorders 541–542
oblique lines 71, 300
occupational disorders 617–637
acroosteolysis 442
from footwear 667
keratins 85
nail plate growth 19–20
nail protection against 638
radiodermatitis 700–701
ochronosis 252, 544
oculodentodigital syndrome 230
oculotrichodysplasia syndrome 230
Oland bodies 12
odontomircronychial dysplasia 230
odontoonychodermal dysplasia 223
odontoonychodyplasia with
alopecia 231
odontotrichomelic hypohidrotic
ectodermal dysplasia 230

O
odontotrichoungual digital palmar syndrome 231
oil patches 81, 448–449, 453
causes listed 910
oils, nail massage with 86
Ollier disease 195, 749
chondrosarcoma from 759
Olmsted syndrome 223, 443
omega nail 61, 62
one-hand/two-feet tinea syndrome 351
ongle en fermoir de nourrice 61
ongle équisegmenté hyperazotémique see uremic half-and-half nail
onion-ring appearance, implantation epidermoid cysts 182
onychauxis 68
causes listed 937
onychia punctata see pitting
onychoatrophy 67
idiopathic atrophy of the nails 76, 419, 422, 423, 424
onychoclavus (heloma) 343, 666–667, 668
Onychocolla canadensis 340
onychocorneal band 2, 4
onychocryptosis see ingrowing nails
onychocytic carcinoma 699
onychocytic matricoma 688–689, 699
onychodermal band 1–2, 4, 498, 541
onychodynia 576
onychogryphosis 68–70, 241–245
causes listed 938–939
ectodermal dysplasia with 235
elderly patients 344, 345
gout 543–544
palmoplantar keratoderma with periodontitis and (Haim–Munk syndrome) 70, 221
spinal cord injuries 508
onychoheterotopia 248–249
onycholemmal carcinoma 707
onycholemmal cysts 692, 694–695
onycholemmal horn 677, 678
onycholysis 80–82
alopecia areata 440
Candida colonization 381
causes listed 910–914
from footwear 665, 667
helma 343
lichen planus 418, 419, 420
from manicure 658, 659
nail growth 38
occupational 637
onychomycosis 380
paraneoplastic 548
postoperative 886
psoriasis 81, 170–171, 449, 453
children 304, 305
psoriatic arthritis 460
systemic lupus erythematosus 523
targeted anticaner therapies 610–612
taxanes 607–609
treatment 874
Trichophyton rubrum 352
onychomadesis 78–80
alopecia areata 437
causes listed 939–941
Cronkhite–Canada syndrome 80, 496
erythema multiforme 436
hand–foot–mouth disease 393
idiopathic familial 262
latent 71, 72, 78
lichen planus 309
pemphigus 432
retronychia 862, 863
ultrasonography 145, 146
see also degloving
onychomatricoma J30, 182–183, 184, 695–699
confocal microscopy 206, 208
dermoscopy 126, 136, 137, 208, 697
ultrasonography 158, 159
onychomycoses (fungal infections) 20, 349–389
aging 340–341
AIDS 539
confocal microscopy 205–206
diabetes mellitus 340–341, 501, 505
dialysis 501
differential diagnosis 370
discoloration 88
friable nails 85
hemodialysis 501
histological stains 9
histopathology 365–369
immunodeficiency disorders 317, 356, 358–359, 360
nail growth 39
on nail permeability 43
nail plate keratins 19
non-dermatophyte 381
occupational 632–633
onychomatricoma 696
optical coherence tomography 169–170
pincer nail 62
pregnancy 502
psoriasis vs children 306
renal transplantation 502
symptomless 354, 355
toenails 82
treatments 370–381
non-surgical devices 375–377
surgical 378–380
systemic 374–375
topical 370–373
venous insufficiency 341, 485–486
see also Candida infections
onychomycosis nigricans 369
onychopapilloma 83, 92, 124, 126–127, 136, 689–691
onychophagia 324, 513–514
infections 304
methylphenidate 583–584
warts 675, 676
see also thumb sucking
onychophosis 343, 344, 664, 665
onychorrhexis 70, 84
causes listed 941–943
discoid lupus erythematosus 429
osteoarthritis 515
syndrome with 251
onychoschizia 20, 42, 590
causes listed 943
onychotillomania 70, 135, 324, 514
onychotrichodysplasia with neutropenia 236
opaque trachyonychia 311, 312
alopecia areata 438
operating rooms, policy on nail cosmetics 639
optical coherence tomography 168–170
oral contraceptives 586
orange sticks 622
orf 393, 394, 631–632
orthoses 344, 672
Osler's nodes 483
osteoarthritis 515
mucoid pseudocysts 178, 341, 759
transverse overcurvature of nail 62
osteoblastoma, osteoid osteoma vs 751
osteoartilaginous tumors 743–752
imaging 193
osteochondromas 161, 193, 744, 745, 746
osteochondromatosis see hereditary multiple exostoses
osteogenic sarcoma 756
osteoid fibroma 718
osteoid osteoma 194, 196, 197, 198, 750–751
osteolysis 35
osteomyelitis, chronic recurrent multifocal 516
osteonychodysplasia see nail–patella syndrome
osteophytes
  mucoid pseudocyst 179–180, 762, 763
ultrasonography 164
osteopoikilosis 263
osteoporosis 340
acroosteolysis with 246
osteonchoperoneal syndrome 216, 246
otopalatodigital syndrome type 1 247
oven-cleaning foam 629
overcuring, acrylic nails 655
overcurvature 248
parrot beak nails 64
transverse 61–62, 68
oxaboroles 372–373
oxalate granuloma 766
oxalic acid 628
oxalosis 542
oxygen inhibition layer, acrylic nails 654
oxytetracycline 578

p
P-3058 (terbinafine nail solution) 373
p-tertiary butylphenol formaldehyde resin 626
pachydermoperiostosis 60
autosomal dominant 246
autosomal recessive 246
pachyonychia 68, 241–245
acquired monodactylous longitudinal 695–699
pachyonychia congenita 68, 83, 227–238, 239, 252, 307
alopecia 28
with amyloidosis and hyperpigmentation 224
keratin 17
with leukonychia 225
pachyonychia congenita-K6A (PC-K6A) or PC3 224
pachyonychia congenita K6B (PC-K6B) or PC4 224
pachyonychia congenita-K6C (PC-K6C) 224
pachyonychia congenita-K16 (PC-K16) 223
pachyonychia congenita-K17 (PC-K17) 223
Pacinian neuroma 739
Pacinian schwannoma 741
packing, ingrowing nails 854
paclitaxel, onycholysis 607
pagetoid pattern, melanoma 780
pain
  acroosteolysis 442
  aging, foot 337
  Bowen disease 136
  chondrosarcoma 196
  complex regional pain syndrome 512
  congenital absence of 508–509
  congenital hypertrophic lip of the hallux 327
  congenital insensitivity to 258, 509
cryosurgery 864
cryotherapy 679
end-stage renal disease 315–316
end-stage renal disease 315–316
  giant cell tumors of bone 751
  glomus cell tumor 137, 185, 187, 731–732
heloma 343
herpes simplex 392
hydrofluoric acid 628
implantation epidermoid cysts 693
incontinentia pigmenti 267, 687
intralesional therapy 457
intraoperative 885
laser therapy 458
lichen planus 418
malnutrition 541
mucoid pseudocysts 180
neodymium:ytrrium–aluminum–garnet lasers 377
osteoid osteoma 750
paronychia 395
perionychial tissues 83
pharmacodynamic therapy 377
photopheresis 576
pincer nail 338, 861
postoperative 887–888
preoperative explanation 827
ptyerygium inversum unguis 77
spinal cord injuries 508
taxane onycholysis 607
trumpet nail 62
tuberculous sclerosis complex 255
palmar arch 22–23
palomplantar and disseminated porokeratosis 260
palomplantar keratoderma (PPK) 227, 443
  and alopecia 221
  with atrophic fibrosis of the extremities 222
  cardiomyparylated with woolly hair and 217
  and clubbing of nails 222, 246
  with cystic eyelids, hypodontia, and hypotrichosis 226
  with leukonychia and deafness 221
  mutilans with deafness 221
mutilating with periorificial keratic plaques 223, 443
  with nail dystrophy and hereditary motor–sensory neuropathy 222
Olmsted syndrome 223, 443
pachyonychia congenita 233
papulosa of Buschke–Fischer 221
  with periodontitis and onychogryphosis (Haim–Munk syndrome) 70, 221
  with periodontosis of Papillon–Lefèvre 221
  progressiva of Meleda 221
  punctate type 1 221
  of Host–Unna 220
palomplantar keratoderma papulosa of Buschke–Fischer 221
palomplantar keratoderma progressiva of Meleda 221
palomplantar keratoderma punctate type 1 221
palomplantar keratosis 219
palomplantar pustulosis 451
pamidronic acid 588
pan-FGFR inhibitors, selective 611, 613
panonychoma fibropapilliferum 696
papillary adenocarcinoma, aggressive digital 709
papuloeuthroderma 520, 548
paracetamol 887
parakeratosis pustulosa 307–308
parallel microlines 117, 120
paramethadione 250
paraneoplastic syndromes 546–549
carpal tunnel syndrome 510
Castleman disease 518
glucagonoma syndrome 496–497
ischemia 484, 485
lymphoma 520
paraquat 628
parathyroid extract 586
paresis 623, 624, 653
Parkes–Weber syndrome 724
Parkinson disease 513
paronychia 83, 361–362
acute 301–302, 395–396
bacterial infections 362, 629
Candida 381
chronic 314, 362
differential diagnoses 897–900
erythema multiforme 436
etretinate 589, 591
from footwear 665
fungal infections 89
nail sculpturing 654, 657, 658
occupational 636
pemphigus 431, 432
propanidid 624
prosector’s 629–630
proximal subungual
onychomycosis 359
psoriasis 446
targeted anticancer therapies 610
rubberoid arthritis 482
PATEO syndrome 607, 608
PC-2 phenotype, keratins 17
pebbling 504–505
pediculosis 403
peduncles, mucoid pseudocysts 179, 181
peeling skin, syndrome with (PLACK syndrome) 225
pellagra 541
peloprenoic acid 588
pemphigus 431–433
Castleman disease 518
familial benign (Hailey–Hailey disease) 92, 432–433, 435
lymphoma 520
pemphigus vegetans of Hallopeau 432, 433
pen push purpura 513
penicillamine 588
Penrose drain 830
periarteritis nodosa 532–533
periarteriopathy 532–533
periarteriopathy 9
perineuroma 158, 160, 742–743
periodic acid–Schiff stain 827
pericyelial tissues 827
peripheral nerve tumors 846, 847
peripheral nerve injuries 83
conditions modifying 83
reduction 858–860
see also entries beginning periungual...
periosteal chondromas 193
periostitis
reactive 756–757
peripheral heart of Masson 25
peripheral nerve injuries 510–511, 512
see also neuropathy
peripheral nerve tumors 738–743
peripheral vascular disease 341, 484–490
atherosclerosis, nail bed 339
peritoneal dialysis
psuedoclubbing 500–501
reflex sympathetic dystrophy 513
periungual (involved)
Bowen disease 136
see also Hutchinson's sign
periungual erythema 521–522
HIV infection 538
periungual fibrokeratoma 161–162, 184, 185
periungual fibromas 166
tubular sclerosis complex 264
periungual fistula 150–152, 153
periungual pigmentation see Hutchinson's sign
periungual pyogenic granuloma 161, 163, 166
periungual soft tissue reduction 858–860
periungual warts 181
permanent wave chemicals 627
permeability 43–44
pernicious anemia 253
pemiasis 487–488
petinax bodies 10, 11, 339, 340
petaloid nail 61
Peutz–Jeghers syndrome 495, 774
Peutz–Jeghers–Touraine syndrome 246, 253
Pfeiffer syndrome 247
pH, on nail permeability 43–44
phalangeal sarcoma 756–757
Phelan–McDermid syndrome 263
phenazopyridine 584
phenindione 585
phenobarbitone 250
phenol 680
phenolization 672, 856–857
phenolphthalein 589
phenothiazines 583
phylephrine 588
phenytin 6, 250, 252, 575, 583
phleboliths 189
photodermoscopy 114, 115
photodynamic therapy
onychomycosis 377
psoriasis 457
warts 679
photography 105–112
photoonycholysis 81
drug-induced 575–576, 577
hemodialysis 501
porphyrias 544, 576
vandetanib 613
phototherapy
adverse effects 588, 589
psoriasis 457
phototoxicity, vandetanib 613
phylogenetic comparisons 28–32
PIBIDS syndrome see trichothiodystrophy
Picture Archiving and Communications Software (PACS) 111
pigmentation 135, 770
acral 95–96
adrenal insufficiency 505
AIDS 539
argyria 593
chemotherapy 606
chloroquine 582
drug-induced nail changes 135
etnicity 119, 135, 774
ezogabine 583
hydroquinone 587
melanoma 121
mercury 594
minocycline 578
ochronosis 544
onychomycoses 352, 353, 363
paraneoplastic 548
periungual see Hutchinson's sign
phenothiazines 583
Pseudomonas infections 359, 362
syndromes with 219, 224, 236, 256
syphilis 397
vitamin B12 deficiency 541
zidovudine 580–581
see also melanonychia
pili torti
leukonychia with 251
and onychodystrophy 236
pili torti syndrome 263
pin test (Love) 732, 733
causes listed 944
flattening 855
from footwear 665, 666, 670
gastrointestinal disorders 548
implantation epidermoid
cysts 693
pseudo-Kaposi syndrome 737
renal failure 501
surgery 860–862
systemic lupus
erythematous 523
pineal hyperplasia, syndrome with 263
pinta 398
pitting 73–74
alopecia areata 436, 437, 438
causes listed 944–945
lichen planus 417–418
psoriasis 304, 305, 446–447, 449, 453
psoriatic arthritis 460
shiny trachyonychia 312, 313
pityriasis lichenoides acuta 411
pityriasis rosea 411
nail pitting 74
pityriasis rubra pilaris 261, 409–411
HIV infection 539–541
PLACK syndrome 225
plakoglobin deficiency, skin fragility
syndrome with 256
plants 620, 622
plasmacytoma 517–518
plasminogen activator inhibitor 2 17
plasticizers, nail polishes 656
platform shoes, onycholysis 667
pleoptic cameras 107
pleonosteosis 247
plexiform neurofibromas 740
plexiform schwannoma 741
plicated nail 61, 62
Plummer–Vinson syndrome 495
Plummer’s nails 507
pneumonia 494
podiatry 671, 672
podophyllotoxin 587
POEMS syndrome 517–518
poikiloderma
bullous (Kindler syndrome) 225, 258
sclerosing 246
poikiloderma acrokeratotica (Weary
syndrome) 225, 238
poikiloderma with neutropenia,
Clericuzio type 225
poisoning 592–594, 633, 638
nail clippings 575
see also arsenic
polarized light
dermoscopy 114, 115
intraoperative 127–128, 129, 130
see also cross-polarized
photography
poliomyelitis 513
polychlorinated biphenyls 250, 592
polychromia 123, 124, 126
polycythemia vera 516
polypenia hyperplasia, syndrome 83
polyethylene gloves 639
polymerization, acrylic nails
652–653, 655
polyvinyl alcohol gloves 639
polyvinyl chloride 633
glove materials 639
popliteal pterygium syndrome
216, 231
porokeratosis 261, 441
multiple types 260
porokeratosis of Mibelli 441
porokeratotic eccrine nevus
269–270
porphyria cutanea tarda 252, 544, 545
porphyrias 544, 545
photoonycholysis 544, 576
port wine stains 722, 723
posaconazole 370, 375
positioning
MRI 176
photography 108, 109
post processing, photography 111
potassium, cystic fibrosis 298
powders, acrylic nails 652, 653
power tools, microtrauma 619
PRAAS (CANDLE) 259
practolol 584
pre- and postnatal growth
retardation, mental
retardation, and acral limb
deficiencies 244
prednisolone, lichen planus 424
prednisone 587
pregnancy 502, 503
prenal malignant lesions 700–701
premedication 828
premixed acrylic gels 653–655, 656
preoperative assessment,
medications 828, 885
preoperative measures 827–828
press-on artificial nails 657
press-on nail art coatings 656–657
preterm infants
aluminum 40, 298
nail measurements 298
pretibial dominant dystrophic
epidermolysis bullosa or
RDEB 257
pretibial myxedema 763
primary biliary cirrhosis,
clubbing 497
primary nail field 3, 5
primary osteoma cutis
763–764, 765
primates, nails 28
primers, acrylic nails 653
printing workers 624, 625
privacy, photography and
106, 111
progeria 244, 252
progeroid syndrome 244
propacetamol 625
propanidid paronychia
584, 731
propolis 625
propranolol 584, 731
propylthiouracil 587
prosector’s paronychia
629–630
prostate cancer, nail selenium
41
prostheses 344, 880–881
see also artificial nails
protease inhibitors 581
protease-associated
autoinflammatory
syndromes 259
proteins
diet content 298
nail plate 40
proximal digital block 833
proximal nail avulsion 836–838
proximal nail fold 1, 2, 15, 76, 826
biopsy 843
closures of defects 844–846
differential diagnoses 896–902
proximal nail fold (cont'd)
flap dissection 762–763
glomer cell tumor 188
manicure 648
Mohs surgery 850–853
notch 877
psoriasis 446
proximal subungual onychomycosis 357–359, 369
non-dermatophyte 381
proximal white subungal
onychomycosis 357–359
histopathology 367–368
HIV infection 539
pruriginous dominant dystrophic
epidermolysis bullosa 258
pseudo-Hutchinson’s sign 120, 773, 774
pseudo-Kaposi syndrome 725
pincer nail 737
pseudo-Koenen tumors 543
pseudo-pseudohypoparathyroidism 506
pseudo-Recklinghausen intradermal
nevi 784–785
pseudo-TORCH syndrome type 2 259
pseudocaeromegalay 503
pseudoainhum 490, 510
pseudomatrix hernia 490–493
pseudolymphoma, APACHE 729
pseudomacrolunula 886
pseudomaculata 66
Pseudomonas (spp.) infections
381, 629
antibodies 16
artificial nails 639
great toenail 671
nail sculpturing 654
pigmentation 89, 359, 362
psoriasis area and severity
index 454
psoriatic arthritis 445, 453, 460–461
children 307
high-resolution peripheral
quantitative CT 170
psoriasiform nail dystrophy 74
pseudonail 714
psuedopitting 74
psuedoporphrya 501, 576–578
psuedopsoriatric nails 658–659
psuedotumors 759–767
fibroosseous, reactive
756–757
psuedophytomycoses
159–164
psittacosis, splinter
hemorrhages 494
psoralens
adverse effects 588, 589
psoriasis 455
psoriasis 445–462
AIDS 540
antimalarial agents 582
associations 453–454
Beau's lines 38
beta-blockers 462, 584
children 304–307, 445
diagnosis 450
differential diagnosis 453
drugs inducing 575
high-resolution peripheral
quantitative CT 170–171
leukonychia 94, 447, 448
linear 268
lithium 462, 583
nail fold vessels 24
on nail generation 35
nail pitting 74
nail plate keratins 19
onychogramysis 69
onycholysis 81, 170–171,
449, 453
children 304, 305
onychomycoses vs 370, 453–454
children 306
quality of life 454
radiotherapy 44
severity scales 454
treatments 454–460
of exacerbating factors 456
of topical 454–457
ultrasonography 146–147
variants 450–453
vascular supply 23
psoriasis area and severity
index 454
psoriatic arthritis 445, 453, 460–461
children 307
high-resolution peripheral
quantitative CT 170
psoratic onychopachydermoperiostitis 452
PTEN hamartoma syndrome 264, 265
pterygium 76–78
diabetes mellitus 504
leprosy 399, 400
lichen planus 76, 415, 416, 417, 418
from manicure 659
onchotillosoma 514
syndromes with 216, 231, 261
treatment 877–880
see also dorsal pterygium; ventral
pterygium
pterygium inversum unguis 14, 77–78
causes listed 915–916
diabetes mellitus 504
systemic lupus erythematosis 524
systemic sclerosis 527–528
pulp, glomus cell tumor 188
pulse oximetry 588–589
pulsed-dye lasers, warts 680
punch biopsy 839, 840
punching
subungal hematoma 866–867
see also drilling
punctate depressions see pitting
punctate leukonychia 92
geometric 440
pup tent sign 418, 420
purgevatives 589
purple toes syndrome 586
purple-blue spot 125, 126
purpura fulminans 314–315
pushers, manicure 648
pustular psoriasis 450–452
children 307
PUVA phototherapy
adverse effects 588, 589
psoriasis 457
pyknody sostosis 246
pyloric atresia
epidermolysis bullosa simplex
with 256
junctional epidermolysis bullosa
with 257
pyocyanin 89
pyoderma gangrenosum 444
pyogenetic granuloma 72, 190–191,
729–731
atypical vessel pattern 124
etretinate 590
Guillain–Barré syndrome 511
Index

melanoma mimicking 776
melanoma vs 730, 779
periungual 161, 163, 166
radiosurgery 864
targeted anticancer therapies 610
tazarotene 591

q
QT interval prolongation 41
quality of life, psoriasis 454
quaternium-15 625
Quincke's pulse 482–483
quinidine 585
quinolones 579
quitter's nail 494

r
R-spondin 2 6
racket nails 884
hyperparathyroidism 506
see also brachyonychia
racket nerve thumb 63–64
radial nerve block 836
radiation exposure 42, 589, 621, 622
penetration of nail 44
for psoriasis 455, 458
see also ultraviolet radiation
radiodermatitis 700–701
human papillomavirus and 702
radiographs
aneurysmal bone cyst 726
exostosis 746
keratoacanthoma 683
preoperative 827
radiosurgery 863–864
radiotherapy, psoriasis 44
Rapp–Hodgkin syndrome 230
Raynaud phenomenon/disease 23, 489–490
vibration white finger 619
see also white finger syndrome
reactive arthritis 452–453, 534
AIDS 462
rebalancing, artificial nails 653
recessive dystrophic epidermolysis
bullosa 254, 257
recessive dystrophic epidermolysis
bullosa centripetalis 258
recessive dystrophic epidermolysis
bullosa inversa 258
Recklinghausen syndrome see neurofibromatosis type 1
recurrent infantile digital fibroma 717
recurring digital fibrous tumors of childhood 720–721
red comets, tuberous sclerosis complex 264
red finger syndrome 538
red lunula 94–95, 519–520
cardiac failure 483
malignancy 519–520
psoriasis 446
rheumatoid arthritis 531
systemic lupus erythematosus 524
red spots 125, 126, 130
Reed's classification, fibromas 717
reflex digital cameras 107
reflex sympathetic dystrophy 38, 512, 513, 887
see also complex regional pain syndrome
regitabine 583
regrowth 6, 35–36
regular pattern, dermoscopy 117, 120
regulations, formaldehyde solutions 650
Reiter syndrome see reactive arthritis
renal disorders 498–502
children 315–316
nail–patella syndrome 227
renal failure 498, 499–501
nail fold vessels 24
renal transplantation 501–502
children 315
Rendu–Osler–Weber syndrome 253, 516
repair of nails 649, 650
repetitive trauma-induced longitudinal pigmentation 135
respiratory disorders 490–494
poisoning 633
RET inhibitor 611, 613
reticulate acral pigmentation of Kitamura 95–96
reticulate pigmented disorder with systemic manifestations 259
reticulohistiocytosis, multicentric 533, 768
juvenile xanthogranuloma 443, 444, 768
retiform hemangiendothelioma 737
retinal angiomas with hair and nail defects 237
retinoids
adverse effects 589–591
incontinencia pigmenti 687
on nail growth 38
psoriasis 455, 458
retinonychia 78, 80, 854,
862–863
ultrasonography 145–146
rheumatoid arthritis 149–150, 151, 530–532
nail fold vessels 24
rheumatoid nodules 531–532
Rhus dermatitis 622
rice oil, contaminants 250
ridges
nail bed 13–14
nail plate 19, 71
onychommatricoma 696
treatment 877
white color 92
see also longitudinal ridges; transverse ridging
rigidity see stiffness of nail ring block 833
ropivacaine 832
Roseneau's depressions see pitting
Rosselli–Gulinetti syndrome 226
rotigotine 583
round fingerpad sign 528
rounding of nails 35–36
roxithromycin 579
rubber gloves 639
Rubinstein–Taybi syndrome 63, 248
Rud syndrome 263
Rüdiger syndrome 244
rudimentary supernumerary digits 739
s
S100 (marker) 11–12
sagittal plane, MRI 176–177
Salaman syndrome 231
salbutamol 591
salicylic acid plaster 678
salmon patches see oil patches
salon workers 623
education 660
salsalate 584
sandpapered appearance, alopecia areata 437, 438
SAPHO syndrome 451
sarcoid dactylitis 494
sarcoidosis 494
sarcomas 756–759
sartans 585
satellite cysts, mucoid pseudocysts 179
Index

scabies 402–403
leukemia 519
see also Norwegian scabies
scalp, lichen planopilaris 419–421, 423
scalp–ear–nipple syndrome 236
scars 875, 876
hypertrophic 887
see also keloid
nail splitting 874
Schamroth’s sign 60
Schernberg and Amiel flap 848
Schinzel–Giedion syndrome 263
schizophrenia 511
Schoon, D., education of salon workers 660
Schopf–Schulz–Passarge syndrome 226
schwannomas 158–159, 191, 740–741
sciatic lights 110
sclerodactyly 528, 529
scleroderma 147–148
see also systemic sclerosis
scleroderma pattern 317, 521, 526, 530
sclerosant, mucoid pseudocyst 762
sclerosing hemangioma 717
sclerosing perineurioma 743
sclerosing poikiloderma 246
sclerotic fibroma 717, 718
see also storiform collagenoma
sclerotylosis 222
scoggin’s type dyskeratosis congenita 218
Sculptured onycholysis 88, 91, 353, 362
culture 364, 365
microscopy 364, 365
scratching, infections from 303
screening
cystic fibrosis 298
newborns, drugs 298, 502
sculptured nails see artificial nails
sculptured onycholysis 81
scurvy 541
sea urchin granuloma 871–872
seagull pattern, osteoarthritis 178
seal finger 629
sealants, industrial 623–624
sebaceous gland carcinoma 709–710
seborrheic keratosis 137, 687–689
Seckel syndrome type 1 247
secondary intention healing, great toenail 849
secukinumab, psoriasis 455, 459–460
Segal’s triad 576
selective IgA deficiency 535
selective pan-FGFR inhibitors 611, 613
selenium 41
deficiency 542
intoxication 592
self-adherent plastic nails 656–657
sensitizers 622
sentinel lymph node biopsy 875–876
Serratio marcescens 89
severe combined immunodeficiency 535
sexually transmitted diseases
human papillomavirus 701–702
Neisseria gonorrhoeae 392, 396
syphilis 396–398
Sézary syndrome 519
shape memory alloy 855
shredding see onychomadesis
shell nail syndrome 61, 494
described 945
shiny trachyonychia 311, 312, 313
alopecia areata 439
shoe laces 664
shoes see footwear
shoreline nails 73, 575
short nails (brachyonychia) 63, 399, 884
short stature, onychodysplasia, facial dysmorphism, and hypotrichosis 263
shoulder–hand syndrome 484
sickle cell disease 303, 516
silicic acid, colloidal, psoriasis 455
silica 593
Singleton–Merten syndrome 260
sinuses 302
sirolimus 591
Sjögren syndrome 530
skeletal anomalies, syndromes with 240–247
sketization 783, 848, 849
skin fragility syndromes (SFS) 220, 256
PLACK syndrome 225
grafts from 849
skin hooks 830, 837
skin tags, removal 648–649
slaughterhouse workers, microtrauma 619
slings 887
slot machine finger 619
smartphones, photography 106
Smith–Magenis syndrome 261
smoking 493–494
soak-off gels 655
soaking 648, 649
sodium, nail plate 298
sodium bisulfite 637
sodium hydroxide, chemical cauteron 857
soft nail disease 84, 263
SOFT syndrome 263
soft tissue
chondroma 748
histology preparation 8–9
reduction, periungual 858–860
tumors 710–721
softening techniques
biopsy 839
histology 8–9, 366
software, imaging 111
soldering flux, aminoethyl ethanamine 627
solenhorn 34
solenonychia 70
solitary angikeratoma 725
Sotos syndrome (cerebral gigantism) 316, 505
sparfloxacin 580
specimens
biopsies 843
DNA from 41
Mohs surgery 850
spicules, complicating surgery 857, 886
Speckle–variance optical coherence tomography 169
spectral curve analysis, ultrasonography 141
SPENCD (spondyloenchodysplasia with immune dysregulation) 260
spherical fibroma 715
sphingolipidoses 543
spicules, complicating surgery 857, 886
Spiegel–Brooke syndrome and racket nails 248
spikes, distal and lateral subungual onychomykosis 362
spinal cord, trauma 508
spiradenoma 682
hidradenocarcinoma from 709
Spitz nevus 319, 320
Spitz–pigment 95
splitter hemorrhages 14, 122, 123
antiphospholipid antibody
syndrome 532
bacterial endocarditis 484
congenital heart disease 483
differential diagnoses 907–909
high altitude 493
onchopapilloma 690
psittacosis 494
psoriasis 449, 453
Raynaud disease 489
renal failure 500
systemic lupus erythematosus 524
targeted anticancer therapies 612
splitting
aging 339
emollients for 42
lamellar 74–75, 299, 300, 666
longitudinal leukonychia 92
nail fold synchia 879
nail fragility syndrome 84, 85
repair 649
traumatic 873–874
spondins 6
spondyloenchodrodysplasia with immune dysregulation, SPENCD 260
spoon nail see koilonychia
sporotrichosis 382
sports
Beau’s lines 666
trauma 620
squalene 374
squamous cell carcinoma 126, 127, 622, 701–705
acrokeratosis paraneoplastica 546
confocal microscopy 206, 209
Darier disease 435
dermoscopy 130, 209
keratoacanthoma vs 182, 485–486
subungual 196
ultrasonography 164, 168
ultraviolet radiation 44
see also Bowen disease; epidermoid carcinoma
stains
histology preparation 9, 364, 366, 368
nail examination 88
staphylococcal infections
atopic dermatitis 427
meticillin-resistant 298
newborns 304
paronychia 362
steatoacanthoma multiple 17
leukonychia, multiple sebaceous cysts, renal calculi 251
stellate lacerations (fragmentation injury) 866, 869
stem cell markers 6–7
stereophotogrammetry 110
sterile pustular conditions 450–452
steroid sulfatase, X-linked ichthyosis 41, 298
steroids see corticosteroids
Stevens–Johnson syndrome 435
stiffness of nail 83
treatments increasing 86
Still disease, adult-onset 317, 515
stimulator of interferon genes–associated vasculopathy with onset in infancy 315
sting-associated vasculopathy with onset in infancy (SAVI) 260
storiiform collagenoma 264
see also sclerotic fibroma
straight nail nippers 830
strawberry-like tumor, CHILD syndrome 265, 266, 267
strength of nails 42, 83
striated leukonychia with eruptive milia 251
stroke 507–508
stub thumb with racket nail 247, 248
styre–butadiene gloves 639
subcutaneous tissue, ultrasonography 141
subtotal leukonychia 91
subungual abscesses 150–152, 153
subungual calcifications 764–766
subungual cherry hemangioma
137–138
subungual epidermoid inclusions (oncholemmal cysts) 692, 694–695
subungual exostosis 137, 193, 194
ultrasonography 160–161, 165
yellow spot 125, 137
subungual fibroma, tuberous sclerosis complex 264
subungual filamentous tumor 714–715
subungual hematomas 87, 772–773
anticoagulants 585
from footwear 665, 666
melanoma vs 779
release 866, 867, 886
trauma 779, 865–867
ultrasonography 152
subungual hemorrhage 135
blood spots 115, 117
pemphigus 488
targeted anticancer therapies 612
subungual hyperkeratosis 34, 59–60, 82–83, 127
causes listed 914–915
Darier disease 435
with distal triangular plate erosion 123
psoriasis 449, 453
children 304, 306
treatments 454
psoriatic arthritis 460
systemic lupus erythematosus 523
subungual keratosis
lichen planus 418, 421
localized multinucleate distal 689
subungual malignancies 196–199
subungual melanoma 196, 199, 771–777
diagnostic algorithm 775–777
histopathology 779–781
prognosis 785–786
treatments 782–783
subungual seborrhoeic keratosis 687–689
subungual syringoid eccrine carcinoma 709
subungual warts 159–160, 163, 181, 676, 677
subungual warty dyskeratoma 691
Sucquet–Hoyer canals 24
Sudeck atrophy see reflex sympathetic dystrophy
sulfasalazine, psoriasis 455, 459
sulfhemoglobinemia 635–637
sulfonamides 579
sulfur, newborns 298
super U procedure 859
superficial acral fibromyxoma 754–755, 756
superficial black onychomycosis 88, 356, 357
superficial onychomycosis 355–356
superficial spreading melanoma (SSM) 777, 778
spontaneous regression 787
superficial white onychomycosis 85, 88, 355–356, 380
non-dermatophyte 381
superimposed linear lichen nitidus 268, 269
supernumerary digits, rudimentary 739
surgery 825–895
anesthesia see local regional anesthesia
biopsy see biopsy
Bowen disease 704–705
closures of defects 843–850
complications 884–887
cryosurgery 621, 864–865
Darier disease 435
dressings 888
exostoses 747
glomus cell tumor 734–735
implantation epidermoid cysts 694
infantile digital fibromatosis 721
instrumentation 828–830
Koenen tumors 711
melanoma 782–783
mucoic pseudocyst 762–763, 764
objective 825–826
onychomycoses 378–380
osteoid osteoma 751
postoperative pain management 887–888
radiodermatitis 701
squamous cell carcinoma 704–705
warts and 680
see also Mohs surgery
sutures, deformity from 886
Suzuki’s variant, Haneke’s procedure 861
sweat ducts 14
sweat gland carcinoma 708–709
swelling, brittle nails 86–87
swimming pool granuloma (Mycobacterium marinum) 392, 402, 630–631
symmetrical acropigmentation of Dohi 95
syndactyly, drug-induced 575
synechia, nail fold 879
synovial cysts see myxoid cysts
synovial tumors 752–753
synovitis
ultrasoundography 164
villonodular pigmented 753
syphilis 396–398
syringes, local regional anesthesia 832
syringofibroadenoma 682–683
eccrine 682–683
syringoid eccrine carcinoma, subungual 709
syringoma 680–681
syringometaplasia, mucinous 677–678
syringomyelia 507
systematized multiple fibrillar neuromas 740
systemic lupus erythematosus 260, 521–525
nail fold vessels 24, 316, 521, 523, 525
systemic sclerosis 526–530
nail fold vessels 24
poisoning 633
Raynaud disease vs 489
tumors 720–721
see also scleroderma
T-Cell immunodeficiency, congenital alopecia and nail dystrophy 263
T-cell leukemia/lymphoma 519
T-Ring® (tourniquet) 830, 831
T2-weighted images, MRI 176
Tabernaemontana coronaria 622
tacalcitol, psoriasis 455, 456
tacrolimus
atopic dermatitis 429
psoriasis 456
tailors 619
tangential excision, biopsy 840–841
taping, ingrowing nails 854
targeted therapies, anticancer 610–613
tavaborole 370, 372–373
taxanes, onycholysis 607–609
Tax syndrome 237, 239
tazarotene
psoriasis 457
pyogenic granuloma 591
tea picking 75
tea-tree oil 679
telangiectasia
capillary malformations 722, 723
causes 896–897
diabetes mellitus 503
hereditary hemorrhagic 253, 516
hereditary hemorrhagic type 2 253
systemic lupus erythematosus 522
telangiectatic granuloma see pyogenic granuloma
temperature, nail growth rates 38
temporary artificial nails 657
tenasin 17
tendon sheath
fibromas 717
giant cell tumors of 752–753
tendons
ultrasoundography 141
see also extensor digitorum tendon
teratogenicity 250, 575
terbinaine 42, 341, 365, 370, 374
drilling with 380
iontophoresis 377
P-3058 (solution) 373
terminal Syme operation 860
terminal vascular units 201
terminology 1–3
Terry’s nail 92–93, 338, 483, 497–498
causes listed 909
paraneoplastic 548
POEMS syndrome 517
see also apparent leukonychia
tetanus 629, 873
tetracyclines 578, 579
thallium 594
thiazides 587
thickening
aging 338, 339, 341
cuticle 83
Darier disease 433
ichthyosis 142, 143
lichen planus 418, 421
onychogryphosis 68
psoriasis 146, 147, 304, 306, 447–448
retronychia 862–863
solenhorn 34
yellow nail syndrome 38
see also pachyonychia; pachyonychia congenita
thioglycolates 627
thioglycolic acid, for ingrowing nails 855
thiourea 626
thoracic outlet syndrome 509
thorns 871
three-dimensional photography 110
thromboangiitis obliterans 485, 486
thrombocytopenia 516
thumb deformity and alopecia 237
thumb sucking 301
parakeratosis pustulosa vs 308
see also finger sucking;
onychophagia
thymic alymphoplasia 535
thyroid acropathy 316, 507
tile-shaped nail 61, 62
timolol
eye drops 584, 585
for pyogenic granuloma 731
tioconazole 371
tiopronin 592
α-tocopherol, yellow nail syndrome 493
toenails
aging 337, 338
care of 649
diabetes mellitus 503, 504
fungal infections 632
grafts from 880, 882
infantile ingrowing 325–328
lichen planus 418, 419, 421
occupational microtrauma 636
onycholysis 82
pachyonychia congenita 233
photography, positioning 108, 109, 109
trauma from footwear 343, 662–673
see also fifth toe; great toenail;
ingrowing nails;
onychogryphosis
tooth and nail syndrome 231
Fried’s 229
tophi 543
total dystrophic onychomycosis (TDO) 359–361, 369
total leukonychia see leukonychia totalis
toughness 83
tourniquets 830, 831
on glomus cell tumors 732–733
toxic epidermal necrolysis 435
nail degloving 80
toxic oil syndrome 592
toxic shock syndrome 303
trachyonychia
alopecia areata 313, 437, 438, 439
causes listed 947–948
children 311–313
psoriasis 305, 306
lichen planus 313, 418
psoriasis 447
vitiligo 444–445
transillumination 88, 633
transmission mode
photography 110
transonychial water loss (TOWL) 43
transplant recipients
melanoma 782
see also bone marrow transplant;
renal transplantation
transposition flaps
mucoid pseudocyst 764
Tweedie and Ranger’s 860
transposition of the great vessels 482
transheal block 834–835
transverse chromonychia, Kawasaki disease 534
transverse grooves 71–72, 447
transverse leukonychia 73, 91–92
AIDS 538–539
artificial nail coatings 657
etretinate 590
from footwear 666
Hodgkin lymphoma 520
occupational 619
paraneoplastic 548
renal transplantation 502
spinal cord injuries 508
systemic lupus
erythematosus 523
transverse overcurvature 61–62, 68
transverse ridging
artificial nail coatings 657
congenital malalignment of the great toe 326–327
trap door avulsion 836, 837
trapezoidal nails 884
trauma 12, 865–881
from footwear 343–344, 662–673
implantation epidermoid cysts 182, 692–693
longitudinal pigmentation 135
manicure 659
on nail generation 33–34
neuromas 739
occupational 618–621
onycholysis 82
onychomycosis 355
perionychial tissues 83
psoriasis, children 305, 306
spinal cord 508
subungual hematoma 779, 865–867
tumors vs 675
ultrasonography 152–153
see also microtrauma
trazodone 583
trimcinolone
lichen planus 423, 424, 425
psoriasis 457
triangular erosion 123
trichinosis 405
trichloroacetic acid, chemical cauteryization 857
tricho-rhino-phalangeal syndrome I (TRPI) 232
tricho-rhino-phalangeal syndrome II 232
trichodontosseous (TDO) syndrome 231
trichoepithelioma multiple familial type 2 263
trichohepatoenteric syndrome type 2 260
trichohyalin 17
trichomelalgia syndrome 263
trichooculodermal vertebral syndrome 237
trichoodontoonychial dysplasia 232
trichoodontonychial type ectodermal dysplasia(s) 231
trichoonychotic hidrotic ectodermal dysplasias 61
Trichophyton interdigitale 356
Trichophyton mentagrophytes 88
Trichophyton rubrum
AIDS 539
distribution 350
graft-versus-host disease 536
occupational infections 632
onycholysis 352
photodynamic therapy 377
trichothiodystrophy 234, 239–240
non-photosensitive 237
photosensitive 237, 239
with transient immunodeficiency 237
trichrome vitiligo 96, 445
trichuriasis 299
tricyclazole 88
triglycerides, marker 41
trimethadione 250
trimethoprim–sulfamethoxazole 579
triphalangy of thumbs and toes 232
tropics, onychomycoses 349–350
trumpet nail 61, 62
tuberculosis 401–402, 494
prosector’s paronychia 629
tuberosus sclerosis 92, 261
Koenen tumors 710
periungual fibromas 264
tuberculosis complex 255–264
tularemia 631
tulip fingers 622
tumor necrosis factor blockers
tumors 675–770

ulcerative colitis 438–440
ulcerative/bullous lichen

ulcers diabetes mellitus 504

ultrasonography 140–168
ultraviolet cured gels 653–655, 656
ultraviolet light-emitting diode technology 656

urologic malformations 189–190
vardenafil 613
undercutting, acrylic nails 655
ungual biopsy 715
universal acquired melanosis 96
unsaturated polyester resins 626

Urbach–Wiethe disease 543
urea with bifonazole 380
chemical avulsion 378–379
topical therapy 371
uremic half-and-half nail 93, 315, 499–500
differential diagnoses 906–907
vandetanib 452
psoriasis 455, 460

Usure des ongles 66–67

V
V-shaped notch, Darier disease 433
valproic acid 250, 575, 583
Vandenbos’ procedure 858–859
vandetanib 611, 612, 613
variegation 776
varnishes, nail damage 86
vascular malformations 189–190, 191
vascular supply 22–25
Vaseline, MRI 176
Veillonella infection, newborns 303–304
venlafaxine 583
venous drainage 23
venous insufficiency 485–486
onychomycosis 341, 485–486
venous malformations 723–725
ventral pterygium 77–78, 877, 878
postoperative 886
verruca vulgaris see warts
verruciform xanthomas 543, 767
verrucous carcinoma 705–707
verrucous epidermal nevus 691–692
inflammatory linear 268
versican 17
vertical stabilization of the fifth

toenail 884, 885
vesiculopustular impetigo 302
vibration 619, 633
victualer’s thumbnail 621
Vieira sign 432
villonodular pigmented

synovitis 753
vimentin 17
vinyl chloride 442, 592, 633
viral infections 390–395, 631–632
in AIDS 539
paronychia 301–302
virucidal agents 580–581
warts 678
vitamin(s), for brittle nails 87
vitamin A deficiency 541
vitamin B12 deficiency 541
vitamin C 587
deficiency 541
vitamin D derivatives, psoriasis 455, 456
vitamin E, yellow nail syndrome 493
vitiligo 96, 444–445
Vohwinkel syndrome 221
Volkman syndrome 484
volume measurement 37
voriconazole 582
VT-1161 (antifungal) 375

W
walking (gait) 662–663
walnut pickers 635
warfarin 250, 586
warts 181, 392, 675–680, 827
AIDS 539
cryosurgery 864–865
management 678–680
occupational 632
radiosurgery 864
subungual 159–160, 163, 181, 676, 677
warty dyskeratoma, subungual 691
washboard nail plates 73, 324

"ulcerative colitis 438–440
ulcerative/bullous lichen

ulcers diabetes mellitus 504

ultrasonography 140–168
ultraviolet cured gels 653–655, 656
ultraviolet light-emitting diode technology 656

urologic malformations 189–190
vardenafil 613
undercutting, acrylic nails 655
ungual biopsy 715
universal acquired melanosis 96
unsaturated polyester resins 626

Urbach–Wiethe disease 543
urea with bifonazole 380
chemical avulsion 378–379
topical therapy 371
uremic half-and-half nail 93, 315, 499–500
differential diagnoses 906–907
vandetanib 452
psoriasis 455, 460

Usure des ongles 66–67

V
V-shaped notch, Darier disease 433
valproic acid 250, 575, 583
Vandenbos’ procedure 858–859
vandetanib 611, 612, 613
variegation 776
varnishes, nail damage 86
vascular malformations 189–190, 191
vascular supply 22–25
Vaseline, MRI 176
Veillonella infection, newborns 303–304
venlafaxine 583
venous drainage 23
venous insufficiency 485–486
onychomycosis 341, 485–486
venous malformations 723–725
ventral pterygium 77–78, 877, 878
postoperative 886
verruca vulgaris see warts
verruciform xanthomas 543, 767
verrucous carcinoma 705–707
verrucous epidermal nevus 691–692
inflammatory linear 268
versican 17
vertical stabilization of the fifth

toenail 884, 885
vesiculopustular impetigo 302
vibration 619, 633
victualer’s thumbnail 621
Vieira sign 432
villonodular pigmented

synovitis 753
vimentin 17
vinyl chloride 442, 592, 633
viral infections 390–395, 631–632
in AIDS 539
paronychia 301–302
virucidal agents 580–581
warts 678
vitamin(s), for brittle nails 87
vitamin A deficiency 541
vitamin B12 deficiency 541
vitamin C 587
deficiency 541
vitamin D derivatives, psoriasis 455, 456
vitamin E, yellow nail syndrome 493
vitiligo 96, 444–445
Vohwinkel syndrome 221
Volkman syndrome 484
volume measurement 37
voriconazole 582
VT-1161 (antifungal) 375

W
walking (gait) 662–663
walnut pickers 635
warfarin 250, 586
warts 181, 392, 675–680, 827
AIDS 539
cryosurgery 864–865
management 678–680
occupational 632
radiosurgery 864
subungual 159–160, 163, 181, 676, 677
warty dyskeratoma, subungual 691
washboard nail plates 73, 324
water content 40, 42, 43
water exposure 74–75
waterless manicure 649
Weary syndrome 225, 238
Weaver syndrome 244
webspace blocks 835
wedge excision, ingrowing nails 857
Wegener granulomatosis 532
Werner syndrome 244
Weyers syndrome 228
white balance, photography 107–108
white spots, from manicure 658
white finger syndrome 489
see also Raynaud phenomenon/disease
white spots, from manicure 658
HIV infection 539, 540
Hutchinson's melanotic 781
Williams elfin facies syndrome 244
Wilson disease 253, 498
wing block 833, 834
Wiskott–Aldrich syndrome 535
Witkop syndrome see tooth and nail syndrome
Wnt signaling pathway 6
Wood's light 88
woolly hair
dilated cardiomyopathy and palmoplantar keratoderma 217
skin fragility syndrome with 256
worn-down nails 66–67
wrist block 835–836
yellow nails
AIDS 538–539
everolimus 612
lymphedema with 260
occupational 634, 635
yellow spot, subungual exostosis 125, 137
yellow-green nail
diabetes mellitus 504
psoriasis 447
Yunis–Varon syndrome 242
zidovudine 580–581
Zimmerman–Laband syndrome 216, 261
zinc deficiency 318, 541–542
Zinsser–Engman–Cole syndrome (dyskeratosis congenita) 85, 218, 238–239, 240, 535
Zook's procedure 861–862