Updates in Clinical Dermatology
Series Editors: John Berth-Jones · Chee Leok Goh · Howard I. Maibach

Robert L. Baran *Editor*

Advances in Nail Disease and Management

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Advances in Nail Disease and Management

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Foreword

Dermatology has been concerned in recent decades about its diminishing domains, such as losing –in many countries – venereology. Yet, the field rose in the minds of many individuals and academic departments. Physicians today benefit from an actually expanding number of diseases and their pathophysiology – facilitated by the increasing number of dermatologists worldwide, remarkable modern technologies including molecular medicine, and the power of the internet, as well as the convenience of Dr. Google.

No one physician or department can master every field, because the information increases almost exponentially, so that if one were to read all of the new information related to dermatology, it would require 34 hours of reading weekly – not readily accomplished.

Nail disease has long been a neglected/unloved arena in dermatologic medicine. Few dermatologists have received extensive training in this large area, with its many connotations to other organ systems, and the same holds true for most academic departments. There are few options to get hands-on learning, such as the American Academy of Dermatology and the European Academy of Dermatology – both sidelined for the moment during COVID.

Fortunately, Robert L. Baran has dedicated his career, from an unusual domain, private practice in the South of France, to master this field – and to make it available to physicians and other healthcare workers worldwide. His standard magisterial textbook (in its many editions) has helped many of us, who have it available. This issue dedicates itself to one important part – recent advances. We hope that Dr. Baran will help us again in the next several years, as it is likely that this volume will stimulate many dermatologists to dig more deeply and expand the field.

University of California School of Medicine
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Howard Maibach, MD

Preface

It would have been more than difficult for one dermatologist to write this book. Science is effervescent with many facets. One person, working alone, cannot delve into and elaborate each.

Consequently, the choice of chapter authors has allowed me to offer the reader updates in a very difficult field, THE NAIL.

THE NAIL is too often ignored or by many physicians considered as an "accessory."

Cannes, France — Robert L. Baran, MD

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Yellow Nail Syndrome

1

Robert L. Baran and Stéphane Vignes

Described in adults by Samman and White in 1964 [1], the yellow nail syndrome (YNS) presents as a triad: yellow nails, lymphedema, and pleural effusions [2].

Yellow Nails

1. Systemic drugs such as bucillamine, gold, methotrexate, penicillamine, and tiopronin are possibly associated with YNS [3]. A thorough drug history should be available for potential drug association followed by discontinuation of the offending agent.
2. Exposure to titanium dioxide (found in foods, personal care items, medications, dental and surgical devices [4]) is associated with YNS and has been detected in the nails [5].
3. Association with a paraneoplastic disease is still controversial, and some consider it a coincidental event. The YNS-to-cancer-diagnosis interval ranges from days to years, with gradual development of the complete YNS triad.

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Various types of cancers have been associated with YNS such as the following:

Breast	Melanoma
Bronchial carcinoma	Multiple myeloma after hematopoietic stem cell transplantation
Endometrium	Non-Hodgkin lymphoma
Gallbladder	Renal cell carcinoma
Larynx	

Yellow nails are the main clinical manifestation (88% of the cases) leading to YNS diagnosis. However, the time between the first clinical sign and nail discoloration hinders affirmation of the YNS diagnosis. Early in the YNS course, YNS is more frequently associated with pleural effusion and lymphedema than in patients with drug-related YNS.

Xanthonychia is unsightly and varies from pale yellow (Fig. 1.1) to a more or less dark (Fig. 1.2) and greenish color.

The nail plate becomes thickened with enhanced transverse overcurvature, sometimes with a notable hump and cross-ridging with a hard (″Scleronychie″ syndrome of German authors) and difficult-to-trim nail plate. Onycholysis may be followed by nail shedding.

The cuticle may disappear leading to erythema of the proximal nail fold causing a chronic paronychia. The lunula is no longer visible due to nail hyperkeratosis. Interestingly, the nail grows half as fast and twice as thick.

The color of the nail is due to lipofuscin, a pigment arisen from colorless lipid precursors and

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Fig. 1.1 Pale yellow nails in YNS

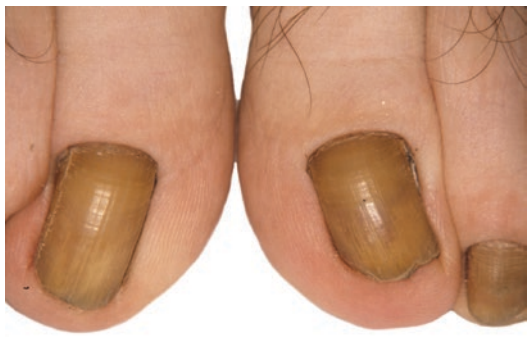

Fig. 1.2 Dark yellow nails in YNS

transformed by oxidation in tissue to produce varying degrees of yellow.

Contrasting with xanthonychia of the YNS that often improves without specific therapies [6] *in about one-half of patients but may relapse, the other varieties of yellow nails are transient* [7].

Specific investigations should be performed:

Rule out nail fungal or *Pseudomonas* infection
Complete blood count
Urinalysis and evaluation of proteinuria
Immunoelectrophoresis
Thyroid-stimulating hormone
Waaler-Rose test for serum rheumatoid factors
Chemistry profile with blood creatinine
Sinus and chest radiography and CBCT
Ear, nose and throat and pulmonary investigations
Liver enzymes and alkaline phosphatases

If the YNS is restricted to nail involvement, the following treatment algorithm should be considered:

- Fluconazole 300–400 mg weekly, associated with alpha-tocopherol (1000u daily) for best results.
- Intra-matrix triamcinolone once per month especially if there is a chronic paronychia.
- Zinc (300 mg/day) may be effective.
- Clarithromycin 300–400 mg daily.

These treatments can be in addition to those used for lymphedema and respiratory disorders.

Lymphedema

Lymphedema is observed in approximately 40% of cases and involves mainly the lower limbs. The face is rarely affected and the eyelids are only exceptionally. The most distal body parts are always more severely affected than proximal parts. Characteristic of lymphedema is the disproportion between lymphatic fluid and the capacity of lymphatic vessels. Stemmer's sign that shows the inability to pinch the skin on the dorsal side or the base of the second toe is pathognomonic.

Manuel lymphatic drainage on each leg for 45 minutes daily followed by placement of a multilayer compression bandage on each leg induced a slight improvement after 1–3 weeks of treatment followed by a compressive garment to stabilize lymphedema volume. In some cases, addition of a low-pressure compression pump may be useful [8, 9].

In cases refractory to conservative management, surgery has been proposed for moderate cases using excision of edematous subcutaneous tissue down to the muscle fascia with skin flaps used as closure. For severe and rare cases, resection of all edematous tissue to muscle fascia with skin grafting taken from the excised tissue has given good results [3].

Respiratory Disorders

The most common respiratory manifestations of YNS are, in descending order, chronic cough, bronchiectasis, pleural effusion, recurrent pneumonia, and restrictive lung disease (mainly due to the presence of a pleural effusion).

Acute or Chronic Rhinosinusitis

Acute and chronic rhinosinusitis are very common and present with daily mucopurulent rhinorrhea, nasal obstruction, and frequent postnasal drip. Acute sinusitis is treated with antibiotics such as *amoxicillin*, *clavulanate* (1.5–3 g/day), *doxycycline* (200 mg/day), or *fluoroquinolone* (levofloxacin 500 mg/day, moxifloxacin 400 mg/day); a surgical procedure such as *meatal antrostomy* may be necessary.

Pulmonary Manifestations

Chronic cough is certainly the most common pulmonary manifestation. *Physiotherapy* training helps patients self-manage their chronic expectoration [6].

Pleural effusions are bilateral in 68.3%. The appearance of the fluid is serous in 75%, milky (chylothorax) in 22%, and purulent (empyema) in 3.5%. Pleural effusions were described as an exudate in 95% and transudate in 5%. For nonmalignant effusion, *tetracycline* is the most practical option.

OK-342 [10], a hemolytic streptococcal preparation treated with penicillin, has been used successfully in Asia. Octreotide 30 mg, once a month, and lanreotide have generated positive response.

Pleural effusions and lymphedema, refractory to conservative management, can be treated with more invasive procedures: chemical pleurodesis, "PleurX® catheter," and pleurovenous shunt all appear to be most effective [11].

Bronchiectasis

Chest CT scan is the best tool for examination. Management includes antibiotics and bronchodilators. Antibiotics used are azithromycine 250 mg × 3 times weekly or clarithromycin 400–600 mg/day for some years.

Recurrent Pneumonia

Vaccinations against flu and pneumococci are highly recommended. Bilateral apical fibrosis and patchy alveolar disease are rarely encountered.

Pulmonary function studies are usually normal or may show a moderate-to-severe restrictive syndrome owing to pleural effusions.

YNS in Children

Pediatric forms of YNS are rarely reported [12]. YNS may be congenital (present at birth) or develop before the age of 10 years. Familial forms of YNS have very rarely been described, affecting two siblings or a family with eight cases in four sibships over two generations. There are very few reported familial cases which mimic a dominant inheritance pattern, but they have not been supported by any genetic evidence. In very rare cases, YNS may be associated with intellectual disability or fetal hydrops, suggesting a more complex syndrome [13].

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2 Is Periungual Vitiligo an Intractable Localization?

Dalia Ahmed Bassiouny and Samia Esmat

Why Are Periungual Vitiligo Lesions Difficult to Treat?

Acral lesions and lesions over joints are usually resistant to medical treatment, and their response to surgical management is often disappointing [1, 2]. Few theories were suggested for explaining the resistance of acral areas to therapy. The well-known one is the lower density or the absence of pilosebaceous follicles, the reservoirs of melanocytes, combined with a higher incidence of koebnerization over these sites due to repeated friction [3]. The constantly poor response to surgical treatment even after supplying melanocyte reservoir in different forms of tissue or cellular grafting suggested the presence of other factors behind the resistance of this area to therapy.

Whether an underlying structural or physiological difference in acral skin induced this resistance to therapy was explored by the research team at Cairo University through a series of publications [3–5]. It was found that acral vitiligo skin was significantly different from the clinically responding vitiligo skin in several aspects, namely, a lower density of both pilosebaceous follicles and perilesional melanocytes and a higher density of sweat glands. Immunohistochemically, acral skin lesions showed significantly lower stem cell factor (SCF), c-kit, MHCII expression as well as lower density of Langerhans cells (LC) [3] and Matrix metalloproteinases] (MMPs) level [4]. PUVA therapy induced similar immunohistochemical changes in both acral and non-acral skin, with the exception of MMP expression [3, 4]. However, acral skin failed to clinically repigment or become repopulated by melanocytes. This was attributed to the originally lower density of melanocytes, melanocyte stem cell reservoir, and SCF production [3]. PUVA stimulated MMP expression by melanocytes rather than keratinocytes [6]. The absence of the melanocyte reservoir in acral skin [3, 7] may be the cause of the failed upregulation of MMP in response to PUVA in acral skin. Another factor is the thicker acral skin that may impair the ability of UVA to reach the proper depth needed for the MMP production [4].

Fibroblasts affect melanocytes through the production of stimulatory factors such as hepatocyte growth factor, SCF, and basic fibroblast growth factor, which enhance melanocyte growth, survival, and melanogenesis [3], as well as MMPs and their inhibitors, which assist melanocyte migration [8]. They also produce some melanocyte inhibitory factors such as tenascin C [9] and Dickkopf1 (DKK1) [10]. In a study focusing on the role of fibroblast-derived products in vitiligo, a significant elevation in the expressions of tenascin C and DKK1 was found in vitiligo lesions compared to normal controls.

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Acral skin showed a significantly higher level of tenascin C [5]. Tenascin C may enhance detachment and subsequent apoptosis of melanocytes [11] contributing to the melanocytorragy theory in vitiligo [12] through the inhibition of the adhesion of melanocytes to fibronectin [13]. To sum up, periungual lesions are deficient in pilosebaceous follicles, the reservoirs of melanocytes that lead to repigmentation in response to medical therapy. In addition, a combination of lower MMP level encumbering melanocyte migration and higher tenascin C level facilitating their detachment in acral vitiligo lesions makes koebnerization at these friction-prone sites easier and might explain poor response of acral lesions to surgical therapy.

How to Approach a Case of Periungual Vitiligo?

It is important to keep in mind that periungual lesions being apparent greatly affect the quality of life of dark-skinned individuals, especially in certain cultures [14, 15]. The patients are sometimes very motivated to treat these lesions even if they are small and insignificant in the physician's opinion. Based on our personal experience, the disease duration, activity, and size of the lesions all should be taken into consideration when approaching a case with periungual vitiligo lesions (Fig. 2.1).

I. *Early Active Lesions (<6 Months' Duration)*

The resistance of periungual lesions to therapy should not lead to loss of hope in the recovery of those cases. Aggressive therapy early in the onset of the disease in our opinion can improve the outcome in such conditions. It is essential to control the disease activity in cases suffering from periungual vitiligo. Lost melanocytes at this site are extremely difficult to recover; hence, stabilization should be achieved as soon as possible. The use of oral minipulse (OMP) of moderate doses of betamethasone /dexamethasone has been pioneered in India by Pasricha et al. [16] A single oral dose of 5–10 mg of betamethasone or dexamethasone is given on two consecutive days per week with 88%–89% of cases achieving stability in 1 to 4 months [17, 18]. OMP can arrest the progression of vitiligo, without inducing repigmentation [19], which is an essential step for successful repigmentation in the periungual area. In an interesting case report, two cases with recent-onset vitiligo lesions, of less than 3 months, over the dorsum of the hands responded excellently to combined systemic steroids and NB-UVB [20]. Similarly, the authors found an excellent response in cases with periungual lesions if medical therapy and phototherapy were applied during the first few months of the onset of vitiligo (Figs. 2.2 and 2.3).

II. *Late Periungual Lesions (≥6 Months' Duration)*

These cases also need to be stabilized if active. When stability is achieved for 12 months in a motivated patient eager to achieve repigmentation, it is essential to measure the size of the lesions in order to be able to tailor a practical clear treatment plan with the patient.

The main source of melanocytes in spontaneous or medically induced repigmentation is the pilosebaceous hair follicles, which are absent in the periungual site, through vertical migration, or the margins of the lesion from which melanocytes migrate horizontally and substitute for pigment cell losses [21]. However, the usual distance of this migration in vitiligo is about 2–3 mm [22]. Horizontal migration of melanocytes leading to marginal repigmentation can therefore be expected to be effective in small lesions. The use of surgical grafting where remote melanocytes are obtained from normal pigmented skin and transplanted into the vitiligo lesions may be used if vertical and horizontal migration of melanocytes is not expected to produce effective repigmentation [23].

(a) *Small Periungual Lesions (<1 cm in Diameter from the Nail Fold)*

Phototherapy alone is of limited value in acral lesions. In a study by Anbar et al. [1], 79% of

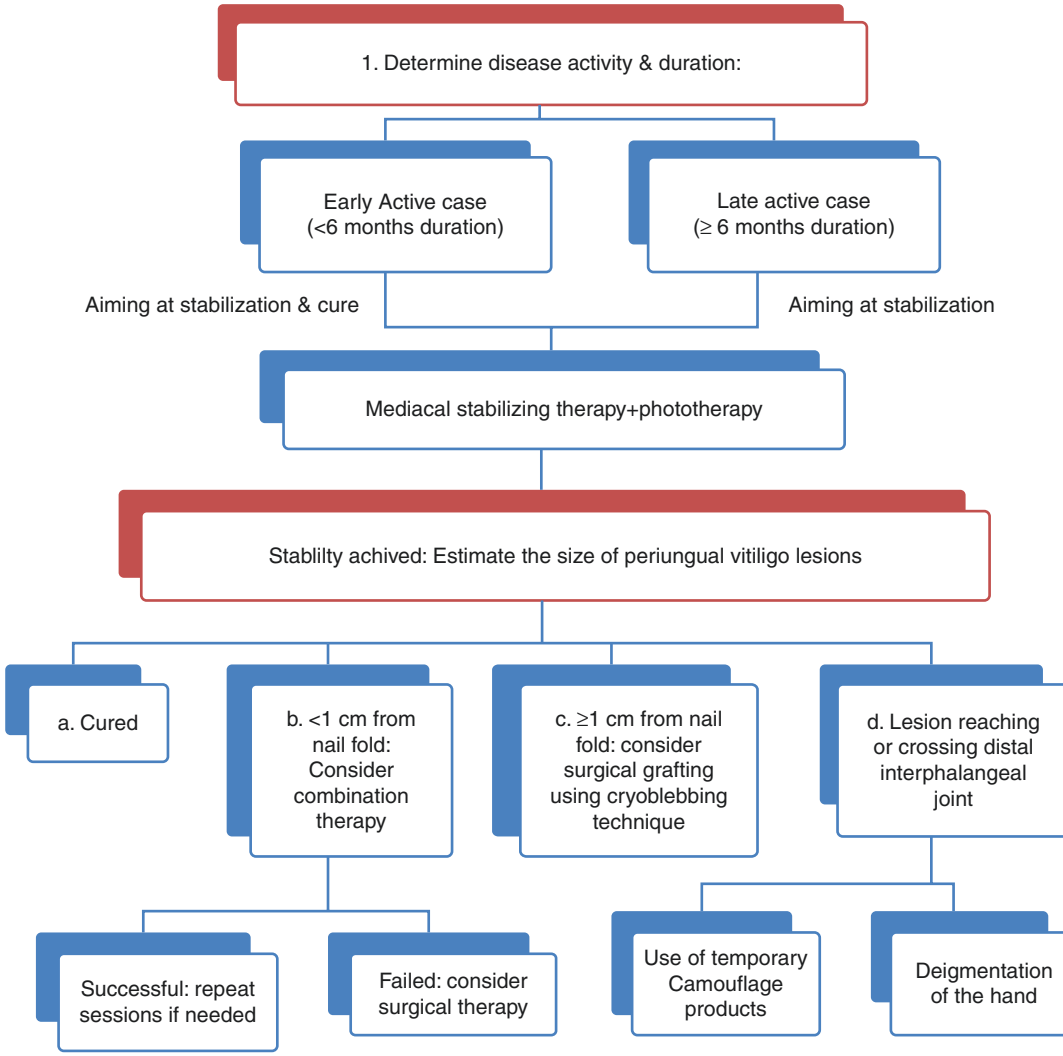

Fig. 2.1 Proposed management plan for periungual vitiligo lesions

cases with acral lesions showed <25% repigmentation, and none achieved >75% repigmentation when NB-UVB was used as monotherapy. Acral lesions showed low response to combined NB-UVB and excimer laser therapy [24]. It was not stated in both studies whether periungual lesions were among those treated. Similarly, acral lesions, including periungual ones, were nonresponsive to both PUVA and UVA1 in a recent study focusing on acral vitiligo [25].

However, combination of different topical, systemic, and light-based therapies could boost the therapeutic response. With the exception of two studies [26, 27], all of these combinations were used in treating cases with a minimum of 12 months' stability of their vitiligo with the extension of the ablative modality a few millimeters into the pigmented skin margin (Table 2.1) [28–33].

Combining erbium-YAG (Er:YAG) laser ablation and 5-fluorouracil (5-FU) application on ablated skin was reported to produce moderate to marked repigmentation in 66.7% of nine cases with periungual lesions [26]. Several passes (usually three) of Er:YAg laser were used to produce pinpoint bleeding which was followed

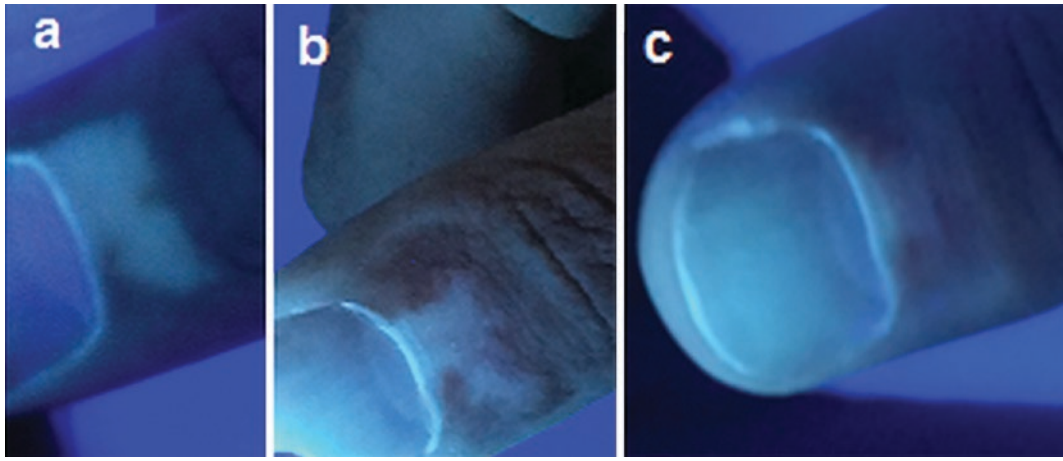

Fig. 2.2 (**a**) An early active case of periungual vitiligo of 4 months' duration before treatment, (**b**) after 6 months of combined steroid oral minipulse and phototherapy showing marginal repigmentation, and (**c**) after 18 months of therapy with 95% repigmentation. (Courtesy of Professor Samia Esmat, MD Department of Dermatology, Cairo University)

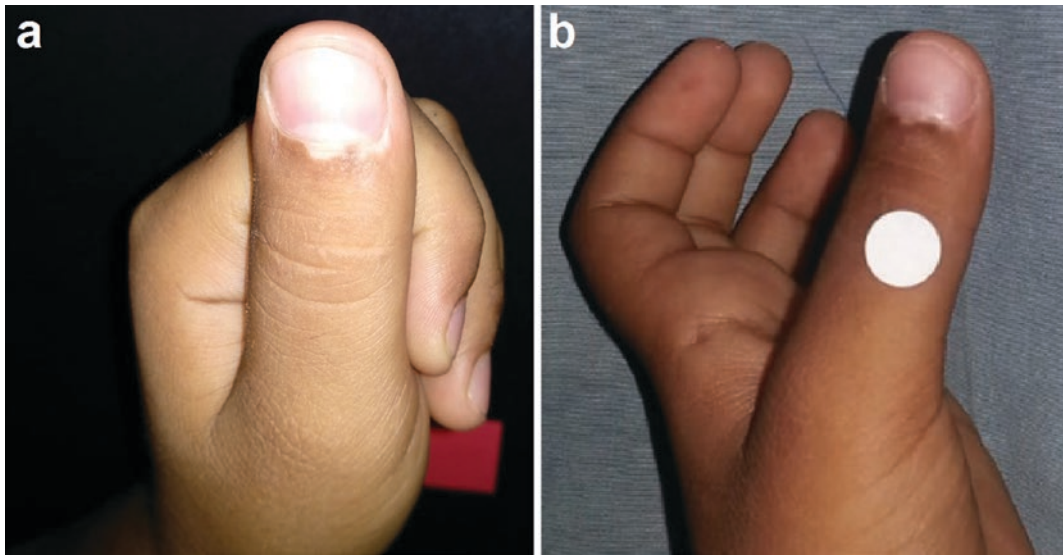

Fig. 2.3 (**a**) An early active case of periungual vitiligo of 2 months' duration before treatment and (**b**) after combined steroid oral minipulse and phototherapy showing complete repigmentation after 6 months of therapy. (Courtesy of Professor Samia Esmat, MD Department of Dermatology, Cairo University)

by topical application of 5% 5-FU cream daily until the inflammation in the form of erythema, moderate oozing, and crustations was achieved. This usually required application for 3–7 days at which point 5-FU application was stopped and topical antibiotic was applied until complete re-epithelization occurred which needed 7–15 days [26]. The use of NB-UVB following a single session of ER;YAg-5FU combination further improved the outcome in vitiligo lesions including periungual sites with minimal side effects [27]. This was the only study in which disease stability was not mandatory based on the precision of the laser beam used, which allowed

Table 2.1 Different studies using ablative therapy, phototherapy, and topical combinations in the treatment of periungual lesions

Authors Study design	No of cases	Technique	Stability (m)	Follow-up(m)	Percentage of repigmentation	Response in periungual lesions	Complications
Anbar et al. [26] RCT intra-patient	9	Treated side: Er::YAG laser dermabrasion+5FU (session repeated 3 weeks after full re-epithelialization until 100% response or three consecutive sessions produce no improvement) Control side: Not treated	Active cases	Not stated	Lesions >75% response Treated side: 33.3% Control side: None	All lesions were periungual	Pain in the treated side
Anbar et al. [27] RCT intra-patient	50	Side A: Er:YAG laser dermabrasion + 5FU + NB-UVB Side B: NB-UVB only	Not stated	4	Lesions >75% response Side A: 43.8% Side B: 7.8%	Finger lesions: Side A: >75% response in 2/9 Side B: None of the lesions >75%	Pain during laser therapy
Mina et al. [28] Comparative intra-patient	25	Side A: Microneedling + 5-FU Side B: Microneedling + Tacrolimus Microneedling extended 2 mm to normal skin. A session/2 weeks for 6 months Topicals under occlusion on the day of the session then once daily	12	3	*Lesions > 75% response* Side A: 48% (40% of acral lesions) Side B: 16% (none of acral lesions)	Not specified in the results Repigmentation achieved in periungual lesions as mentioned in the discussion	32% of %-FU patches (hyperpigmentation, inflammation, ulceration)
Mohamed et al. [29] RCT	64	Group A: Topical % 5FU Group B: Full CO_2 ablation (1/month) Group C: Full CO_2 + 5FU	12	6	*Lesions > 50% response* Group A: 55.9% Group B: 5.7% Group C: 3.3%	Groups A and B none of the lesions showed >50% response Group C: 12/88 of periungual hand lesions >75% response	Pain during laser therapy
Vachiramon et al. [30] RCT intra-patient	26	Side A: FrCO_2 (1/week) + NB-UVB (2/week) + 0.05% clobetasol propionate(2/day) Side B: NB-UVB + 0.05% clobetasol propionate(2/day)	12	3	*Lesions > 75% response* Side A: 23% Side B: 3.9%	Not specified in results but good response in treated periungual sites in photos Side A: Higher mean improvement score in fingers	More pain and edema on laser side

(continued)

Table 2.1 (continued)

Authors Study design	No of cases	Technique	Stability (m)	Follow-up(m)	Percentage of repigmentation	Response in periungual lesions	Complications
Li et al. [31] RCT intra-patient	25	Side A: Fr CO_2 monthly +topical betamethasone solution (under occlusion) + NB-UVB biweekly (6 m) Side B: FrCO_2 + NB-UVB	12	6	*Lesions > 50% response* Side A: 44% Side B: 8%	Not specified in results but good response in treated periungual sites in photos	Moderate pain
Liu et al. [32] RCT intra-patient	126	Side A: FrCO_2 + betamethasone dipropionate(1/month) + NB-UVB Side B: Betamethasone cream + NB-UVB	6	1	Lesions >50% response Side A: 23% Side B: 8%	Not specified in results but good response in treated periungual sites in photos	Pain and edema on laser treated side
Bayoumi et al. [33] Prospective RCT intra-patient	18	*Side A*: 2490 Er laser dermabrasion+ daily hydrocortisone 17-butyrate for 3 weeks/1 week steroid-free + NB-UVB biweekly for 12 weeks *Side B*: Steroid +NB-UVB	Not stated	1	*Lesions > 50% response* Side A; 50% (excellent in 16.7% of lesions) Side B: 4.2%	None of the finger lesions achieved >50% response in any group	Poor tolerance to laser dermabrasion Hypertrophic scar: 2 cases

targeting vitiliginous skin only and the fact that no donor skin was needed which eliminated the possibility of development of koebnerization. Moreover, 5-FU was thought to play a role in stabilizing the disease through its immunomodulatory effect [26].

In a more recent study, a similar favorable outcome was obtained with 40% of acral lesions including periungual ones showed >75% repigmentation when treated by microneedling using a Dermapen at the lowest speed and the needle penetration depth at 0.25–0.5 mm followed by the application of 5-FU under occlusion immediately after microneedling and once daily until the next session. Sessions were done every 2 weeks for a maximum of 6 months. In that report, the authors stressed on the necessity of disease stability before using this technique [28]. On the contrary, CO_2 laser skin ablation followed by 5-fluorouracil application was less effective in inducing repigmentation in periungual lesions than in other lesions on hands and feet [29].

Experimental studies have shown that 5-FU at low concentration selectively destroys keratinocytes within 3 weeks, while melanocytes continue to multiply and produce melanin [34], which was suggested as a means of obtaining pure melanocyte cultures devoid of other non-dendritic epidermal cells [35]. In an animal model in vivo study, only combined dermabrasion and 5-FU resulted in the pigmentation of the whole dermabraded area. It was hypothesized that this combination produced a long-lasting favorable microenvironment for melanocyte migration and pigment spread not created by either modality alone [36]. 5-FU applied on dermabraded skin created selective cytotoxicity on keratinocytes, while melanocytes were relatively spared. The damage of many keratinocytes needed for re-epithelialization delayed healing during the first 2 weeks after the procedure and produced a strong inflammatory reaction including cytokines like leukotrienes C4 and D4 which enhance melanocyte proliferation and migration [37–39]. Furthermore, after 15 days some degenerative keratinocytes could be seen in the lower epidermal layers with the presence of wide intercellular spaces due to the presence of local edema creating an easier route for melanocyte migration. Finally, MMPs are produced during remodeling by keratinocytes which further enhances the migration of melanocytes [40, 41].

The use of fractional CO_2 laser with topical steroids and NB-UVB phototherapy is another combination with promising outcome in this site. It produced better response over the fingers than topical steroids combined with NB-UVB in one study [30] and than fractional CO_2 combined with NB-UVB in the other [31]. In a recent study using this triple combination versus NB-UVB combined with topical steroids in a left-right comparative study, involving 126 cases, it was found to produce ≥50% response in 18% of cases with impressive results over the periungual lesions as apparent from the figures included [32]. No scarring or serious side effects were observed in these three reports [30–32]. On the other hand, a combination of erbium laser dermabrasion, NB-UVB, and topical steroids was less effective with none of the finger lesions achieving >50% response and scarring in two cases [33]. Ablative methods such as fractional CO_2 stimulate the secretion of cytokines and various growth factors during wound healing, which might serve as mitogens for melanocytes [42]. The effect of NB-UVB and topical steroids was enhanced through the removal of the superficial layer of the skin, allowing for a more potent stimulatory effect on melanocytes [43]. Enhancement of the marginal repigmentation was seen when NB-UVB was combined with fractional CO_2 over the peripheral 5 mm of the lesion and adjoining 2 mm of normal skin more than NB-UVB alone [44] which is of great importance in the periungual area as this is the main expected pattern of repigmentation.

(b) *Larger Periungual Lesions (≥1 cm in Diameter from the Nail Fold but not Reaching the Distal Intephalangeal Joint)*

Larger periungual lesions should not be expected to repigment by horizontal migration of melanocytes from the edges even if boosted by the earlier combinations. In stable motivated cases, the transfer of remote melanocytes from

donor skin through surgical treatment remains the only logical way to achieve repigmentation. Surgical grafting techniques for vitiligo include several tissue grafting or the more recently introduced cellular grafting techniques like non-cultured melanocyte-keratinocyte transplantation procedure (MKTP) [45].

Fingers and toes responded well to MKTP with 42% of lesions achieving ≥95% repigmentation in one report [46]. However, it was not clear if any of those lesions were periungual. Similarly, >75% repigmentation was achieved in 42% (8/19) of finger and toe lesions with MKTP. Only four lesions, all of which were periungual, showed <50% response [47]. Some authors avoid treating periungual lesions owing to the poor response [48, 49].

Dermatologists are faced with technical difficulties when surgical treatment of the periungual area is attempted. The epidermis of the thick skin over the digits has an additional layer of dead keratinocytes called the stratum lucidum located between the stratum granulosum and the stratum corneum [50], which may explain why dermabrasion or laser resurfacing at this site to prepare it for suction blister grafting or MKTP is difficult.

Injection of the suspension into blebs created by liquid nitrogen earlier was the technique used by Gauthier and Surléve-Bazeille in 1992 [51] in the first description of non-cultured autologous MKTP. Using this technique, periungual vitiligo lesions fully repigmented in one case in which cryoblebbing was used for recipient site preparation [52]. In a study comparing cryoblebbing to laser resurfacing for recipient site preparation in MKTP: cryoblebbing produced ≥75% repigmentation in significantly more lesions (38 vs. 10 lesions) ($p = 0.001$) mainly due to excellent response achieved in periungual lesions [53].

In an intra-patient comparative pilot study focusing on vitiligo lesions over the fingers, 12 patients with stable non-segmental vitiligo (NSV) affecting the middle three fingers of one hand were recruited. Three variations were used in surgical treatment of the finger lesions: minipunch grafting, melanocyte-keratinocyte transplantation procedure (MKTP) preceded by cryoblebbing, or full CO_2 laser resurfacing of the recipient site. One method was used in each finger (Fig. 2.4). Minipunch grafting was ineffective. MKTP produced >49% repigmentation in 44% of all treated lesions when cryoblebbing was used for recipient site preparation compared to 0% when CO_2 laser resurfacing was used. Repigmentation of ≥75% was seen in four lesions in four different cases when cryoblebbing was used combined with MKTP in various treated sites (one periungual, two over the knuckles, and one phalangeal lesion). Interestingly, the same suspension applied after cryoblebbing periungually and after laser resurfacing of the wrist produced excellent repigmentation in both sites, while no response was seen in the periungual lesion prepared by CO_2 laser in the same patient (Fig. 2.5). This further solidifies the hypothesis that the improved response was due to the use of cryoblebbing in recipient site preparation. Cryoblebbing was more painful than laser resurfacing despite the use of subcutaneous ring block anesthesia and needed more time for complete healing. Color mismatch was seen in 30% of lesions where the repigmentation was darker than the surrounding skin, but that was accepted by the cases [54].

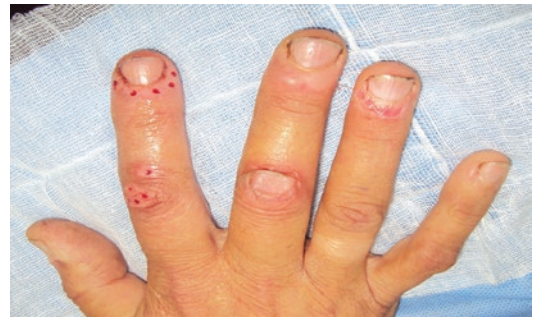

Fig. 2.4 Periungual vitiligo lesions treated by minipunch grafting in the index and melanocytes keratinocyte transplantation procedure of the middle and ring fingers. Lesion was prepared by cryoblebbing into which the cellular suspension was injected in the middle finger while it was applied to CO_2 laser resurfaced lesion in the ring finger

Cryoblebs mechanically produce consistent separation at the dermoepidermal junction regardless of the skin thickness, which ensures

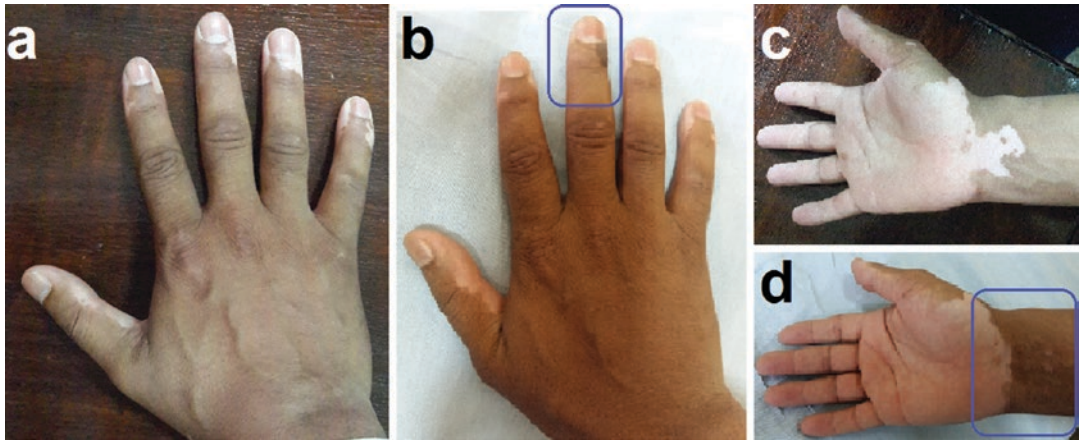

Fig. 2.5 (**a**) Periungual and (**c**) wrist lesions in a stable vitiligo case. Twelve months after treatment with (**b**) excellent response over the periungual lesion in the middle finger treated by cryoblebbing followed by injection of cell suspension into the bleb (blue square) and poor response in the index (treated by minipunch grafting) and the ring finger (treated by CO_2 laser resurfacing followed by cell suspension application) and (**d**) excellent response in the wrist (blue square) treated by CO_2 laser resurfacing followed by cell suspension application in the same session [54]

placing the melanocytes at the required plane for successful grafting. In addition, the roof of the blebs acts as a natural protective dressing keeping the grafted cells in place. Liquid nitrogen application also has immunological effects which are not very well understood. When used for treating warts and tumors, immunostimulation is thought to take the upper hand. Disrupted cells' components act as antigens and stimulate innate immunity Toll-like receptors and dendritic cells which is followed by inflammatory cytokine release, such as IFN δ or TNFα, and antigen presentation by dendritic cells producing attack of tumor or virally infected cells by cytotoxic T cells [55]. In a study using a mouse model with no tumor or virus in its system, tissue necrosis and increased expression of IFN α and dendritic cells were seen following cryoablation without the elevation of IFN δ or TNFα [56]. In addition, cryoablation produced cell apoptosis at the outer rim of the ablation zone which was thought to induce immunological tolerance [57]. It has been proposed that larger numbers of apoptotic cells might cause tissue protection and lead to immunosuppression while larger numbers of necrotic cells could serve as immunostimulators [58].

(c) *Extensive Periungual Lesions Reaching or Crossing the Distal Interphalangeal Joint*

It is important to council vitiligo cases about what to expect from therapy according to his/her case during the first visit. Cases with extensive periungual finger lesions should understand that until now available therapies are inadequate to achieve repigmentation. Cosmetic camouflage can be used in patients with periungual lesions affecting their quality of life and daily activities (Fig. 2.6). Alternatively, the patient may prefer to depigment the remaining areas of normal skin so that the whole hand has a uniform color (Fig. 2.7) [59]. The choice depends on the patient's skin color and culture. In our experience, cases with skin types IV or V prefer camouflage as opposed to appearing odd among their peers. In fair-skinned cases (skin types I and II), regular use of sunblock products for normal skin can reduce the contrast between vitiligo lesions and normal skin making the lesions less apparent with time, which can be satisfactory to the patient.

In conclusion, periungual vitiligo lesions are different from non-acral lesions. They are deficient in pilosebaceous follicles, the most important melanocyte reservoirs in vitiligo.

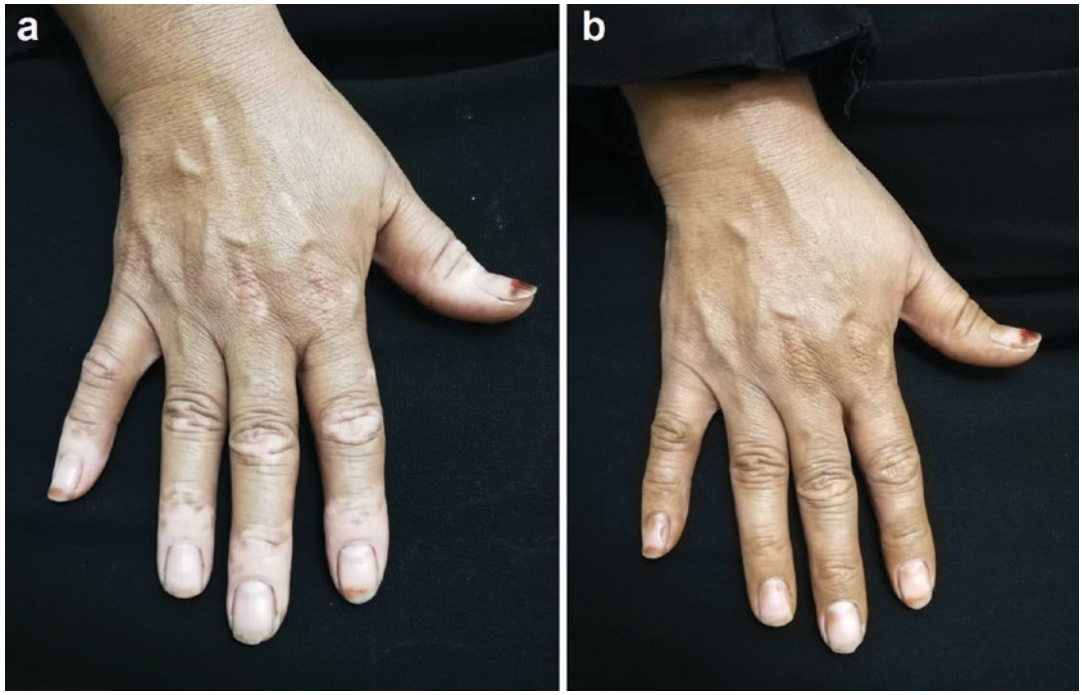

Fig. 2.6 (**a**) Periungual lesions before and (**b**) after the application of temporary cosmetic camouflage

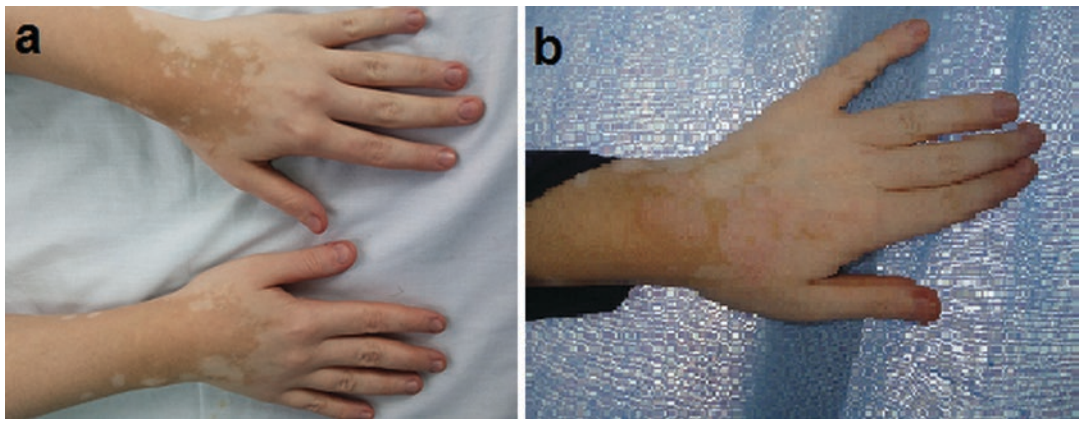

Fig. 2.7 (**a**) Extensive periungual lesions before and (**b**) after depigmentation of the normal areas. (Courtesy of Prof Medhat El-Mofty, MD, Department of Dermatology, Cairo University)

This leads to a lower number of melanocytes which might be reflected in melanocyte/keratinocyte interactions resulting in the other reported differences such as low MMP level and high tenascin C level. Low MMP encumbers melanocyte migration, while high tenascin C facilitates their detachment making koebnerization at these friction-prone sites easier and might explain poor response to surgical therapy. Early aggressive therapy is important in these cases. Enhancement of marginal repigmentation using a combination of ablative, topical, and phototherapies could help improve repigmentation in small-sized lesions, while larger ones could benefit from surgical grafting with technique adjustments to suit this unique site.

Use of cosmetic camouflage and depigmentation of the remaining normal skin are options that should be discussed with patients with lesions markedly affecting their quality of life.

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3 Digital Myxoid Cysts: Ganglia of the Distal Interphalangeal Joint

David de Berker

What Is a Myxoid Cyst?

A digital myxoid cyst (DMC) is a ganglion of the distal interphalangeal joint (DIJ). It represents a pocket of synovial fluid that has escaped from the joint and has chosen an interstitial location for the accumulation and displacement of surrounding structures. Some texts have supported the idea that it is a degenerative entity composed of substance arising from a local connective tissue degeneration. But this interpretation arises from a static histological assessment rather than clinical evaluation and investigation where communication with the joint is the norm. This can be demonstrated by injecting the joint with dye and tracking its passage into the cyst [1] or by MRI [2]. There are instances where the communication cannot be identified, and this suggests it is a fluctuating pathology; when the efflux of synovial fluid diminishes, the hole in the joint capsule may seal, and the cyst may resorb into surrounding tissues. This waning is clinically the case in approximately 20% of smaller cysts over a 12-month period.

The cyst itself is without a formal cell lining reflecting how it arises – purely through the displacement of tissue by the pressure of fluid escaping from the joint. Hence, it is formally a pseudocyst. At surgery, compaction of the adjacent connective tissue can provide what clinically appears as a wall.

Types of Myxoid Cysts

For the purposes of clinical classification and prognostication, there are three types of myxoid cysts, defined by the location of the pocket of synovial fluid (Fig. 3.1). The most common is on the dorsum of the digit, above or slightly distal to the transverse line of the distal interphalangeal joint (Type A) (Fig. 3.2). This can be a simple translucent, grey domed lesion with few symptoms, although sometimes associated with the pain of osteoarthritis in the adjacent joint.

The second most common is one located beneath the proximal nail fold but above the proximal part of the nail plate (Type B) (Fig. 3.3). At this location, it compresses the matrix from above the nail, which is thin and can be indented by the volume of the cyst above it. As the cyst varies in volume according to the amount of fluid escaping from the joint, the indentation on the nail increases. Combining this with the continuous longitudinal growth of the nail creates a timeline of the volume of the cyst, often punctuated by small ladder-like rungs of the transverse ridge. This appearance is very characteristic of myxoid cysts at this location. When the other features are

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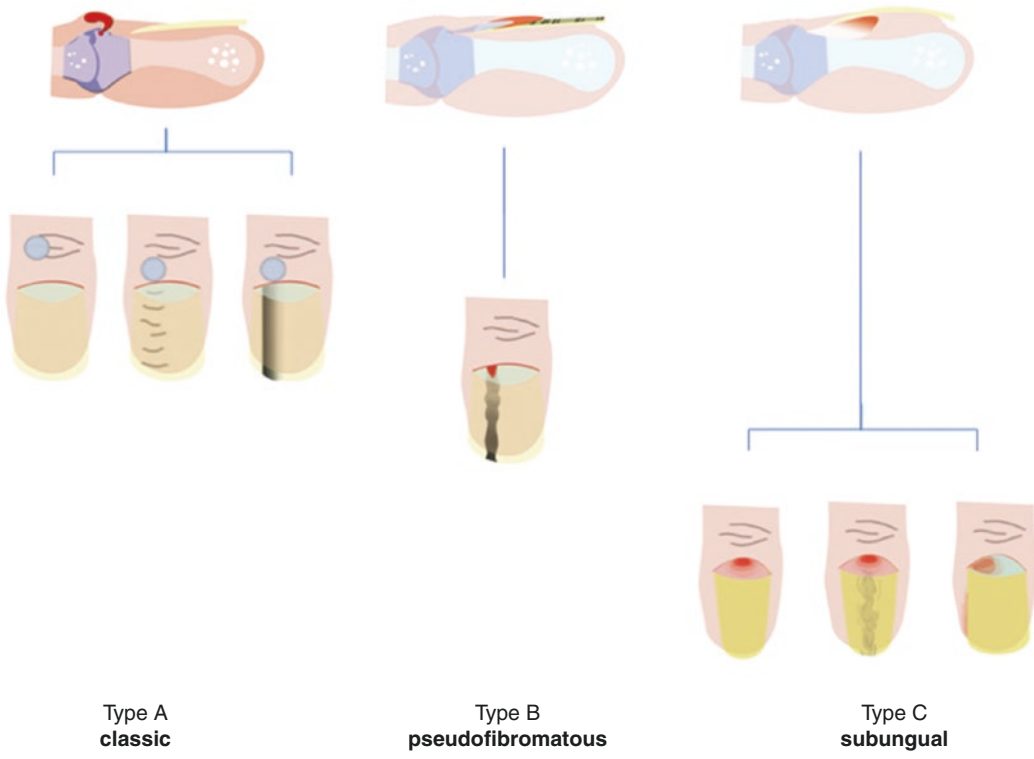

Fig. 3.1 Three variants of myxoid cyst according to the location in relation to the nail unit

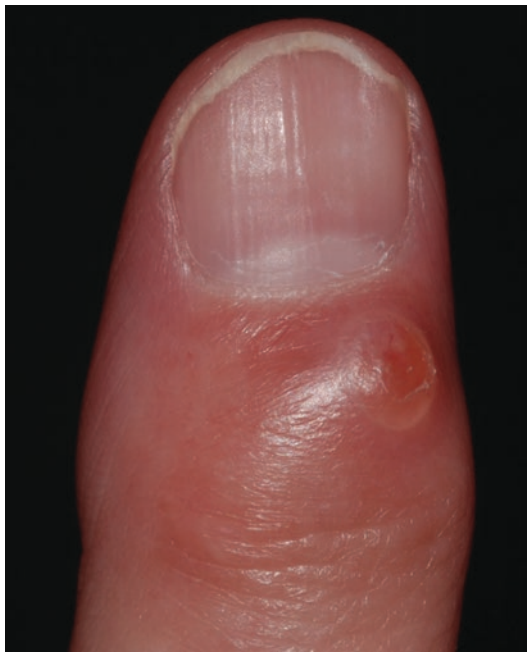

Fig. 3.2 Type A myxoid cyst located on the dorsum of the digit

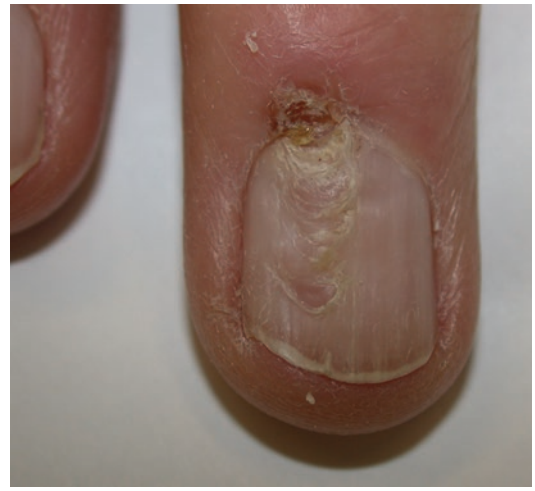

Fig. 3.3 Type B myxoid cyst located beneath the proximal nail fold and above the nail plate, creating a longitudinal groove of fluctuating depth and width

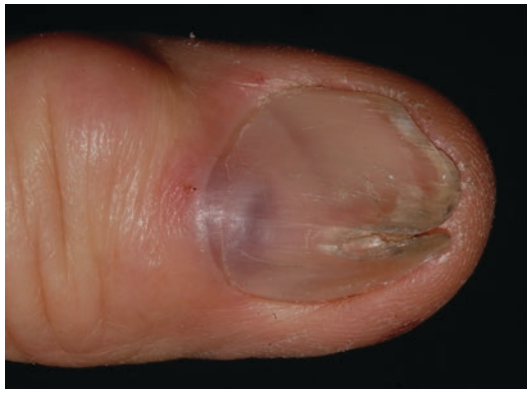

Fig. 3.4 Type C myxoid cyst located beneath the nail matrix with consequent changes in the shape of the matrix and nail growth

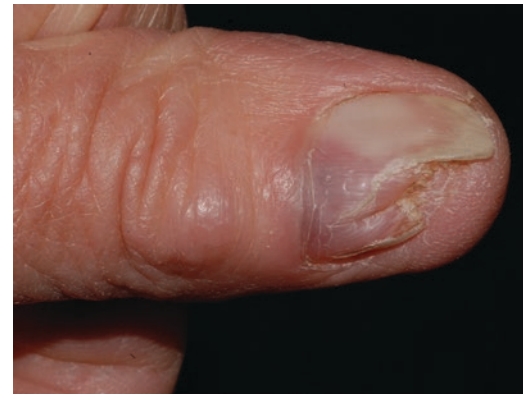

Fig. 3.5 Ingrowing at the distolateral margin of the nail in Type C myxoid can cause pain as a presenting feature, in this instance, in combination with partial destruction of the nail plate and a red lunula

limited to a small crusted or keratinous papule at the margin of the cuticle, the ladder sign can be a significant clue to diagnosis (Fig. 3.3). Episodic escape of a clear gel may also be in the history for Type A or Type B cysts. In Type A, the deflation of the cyst is manifest, and the patient perceives the direct effect. In Type B, it may not be so clear, but over time, the fluctuating longitudinal groove in the nail reflects the change by losing volume, in terms of depth and transverse width.

In rare instances, Types A and B can overlap as a cyst deep within the proximal nail fold, but still just visible on the dorsum of the digit, but deep enough to have an effect on the underlying matrix by pressing on it. In this instance, the longitudinal groove fluctuates less or not at all.

Type C myxoid cyst (Fig. 3.4) presents differently from the other two due to its location beneath the nail matrix. This means that the forces it exerts and in turn the forces upon it are different. It is a space-occupying lesion beneath the matrix, pushing upwards. The initial effect is to increase the transverse curvature of the nail. The pathology is usually of a thumb, and this nail then grows reflecting the distortion created proximally and creates a pincer nail. If the cyst is located centrally beneath the matrix, the effect on the nail may be difficult to distinguish from a classic pincer nail, and the presenting problem may be painful ingrowing at the distolateral free edge (Fig. 3.5). However, two additional features help distinguish from the classic pincer nail. First, the lunula is usually red (Fig. 3.5) reflecting the altered lucency of the underlying tissues overlying the mass of clear gel. The second is that over time, pressure beneath the matrix results in the reduction of nail plate production, to the point where the nail may disintegrate through thinning (Fig. 3.5). However, unlike Type A or B, Type C almost never discharges the content to betray its nature and equally does not deflate to provide the fluctuations seen in the other two types.

Clinical Diagnosis and Differential

The diagnosis is based on the history which varies slightly for the variants but typically is of a smooth periungual mass. However, with the variants, the features highlighted in Table 3.1 illustrate the relevant points.

Imaging

In most instances of Type A myxoid cyst, imaging is not needed. Where the diagnosis is not clear or where there is a pathology with features with a differential diagnosis, imaging may help resolve the matter. This is most common in Type B and C cysts.

Table 3.1 Types of a myxoid cyst, their features and differential diagnosis

Type of myxoid cyst	Points in history	Points in appearance	Differential diagnosis
All	Gradual evolution Age > 40 years (unless trauma) Symptoms vary: none, discomfort, pressure, occasionally painful, associated joint pain Usually dominant digits and dominant hand	Swelling	
Type A	Catches, usually no symptoms Episodic rupture with the release of clear gel sometimes smeared with blood Can disappear over time	Domed, grey, translucent From crease of the distal interphalangeal joint to the margin of the proximal nail fold, rarely midline	Giant cell tendon sheath tumour Dermatofibroma
Type B	Distressed by the appearance of the nail Fluctuating problem A nail can split at times Sense of pressure from mass trapped between nail fold and dorsum of nail Occasional ruptures, but less common than in Type A	Small keratinous papule protruding from the cuticle margin in line with a longitudinal groove of the nail The margin of the cuticle can be altered by the pathology with a small grey bulge Longitudinal groove has fluctuating volume reflected in varied width and depth A nail can split at times and lead to split at the free edge Occasional haemorrhage within the pathology and altered nail give a misleading impression of longitudinal melanonychia and corresponding concern	Periungual fibroma (no fluctuation in volume)
Type C	Typically troubled by change in the shape of the nail and some ingrowing at one of the distolateral margins Nails may have started to disintegrate which is also a concern Sense of fullness and discomfort arising from beneath the nail	Red lunula Increased transverse curvature Midline nail disintegration Distolateral ingrowing The nail overlying the matrix may be soft when pressed with your own thumbnail	Idiopathic pincer nail Other submatrix tumours, e.g. chondroma, fibromyxoma Glomus tumour Melanoma Squamous cell carcinoma

Transillumination

Transillumination is the most simple and cheapest form of imaging and in most instances will give a clear answer immediately within the initial consultation. The LED torch on most mobile phones is the ideal light source as it is "cold", small and intense. The source is placed beneath the digit, and the light is applied to its palmar surface beneath the pathology. Moving the source up and down, the digit will help visualise the structures including the outline of the distal margin of the lunula. A myxoid cyst is hyperlucent in contrast to the normal tissues (Fig. 3.6). In Type B and C (Fig. 3.7) cysts, it can be that the focus of the collection of fluid is not clear clinically but revealed by transillumination. In all types, using the technique on other digits at the same assessment can reveal that the pathology is subclinically present at other distal interphalangeal joints (Fig. 3.8). This is consistent with what we know of DMCs, where osteoarthritis, trauma, time and wear and tear all contribute to failure in the integrity of the synovial capsule. And once it happens in one joint, it is likely that other well-used joints may be suffering similar changes.

Clarity of the assessment is increased if the room is dark, and for photography, the contrast is

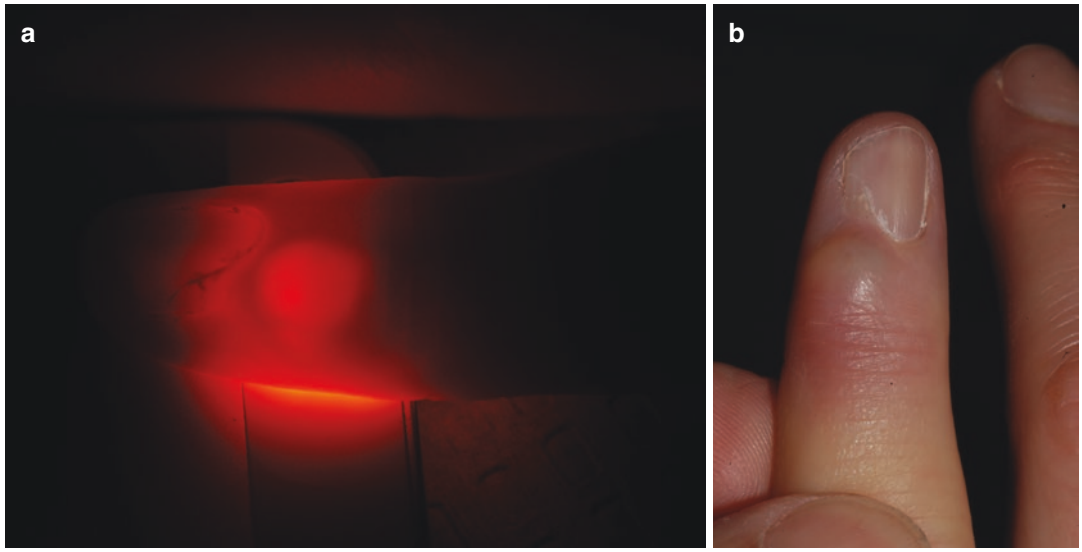

Fig. 3.6 (**a**, **b**) Transillumination of Type A myxoid

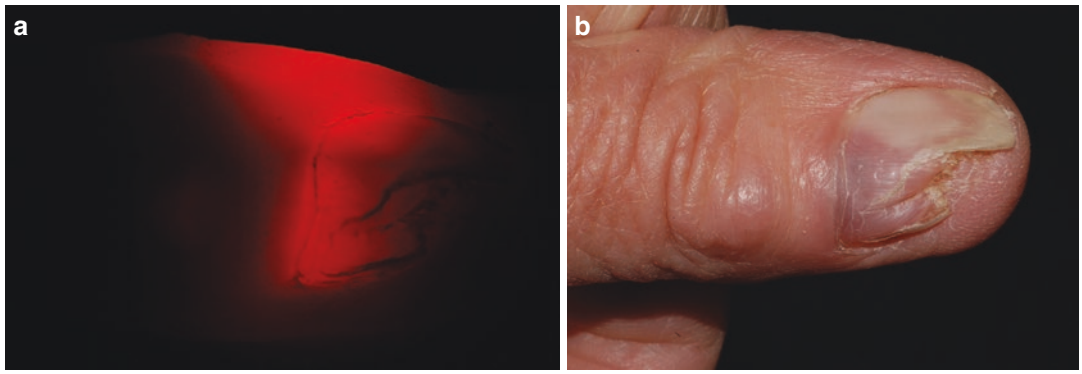

Fig. 3.7 (**a**, **b**) Transillumination of Type C myxoid

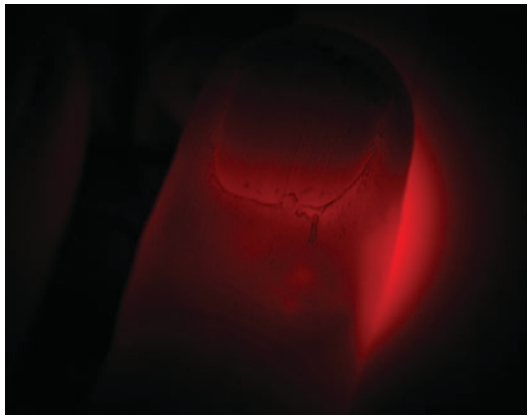

Fig. 3.8 Subclinical myxoid cysts can be demonstrated by transillumination

improved by a darkened room. Warn your patient first of the reason for turning out the lights.

Capturing such images on photography requires relatively long exposures, high ASA and a low f-stop. All these changes make the image vulnerable to the lack of sharpness with fractional movements and grainy resolution of high-ASA exposures. Make sure that the digit is on a stable surface and ideally that the camera is tripod mounted.

Transillumination can also be helpful postoperatively for assessing when there is some residual bulk of the DIPJ. The technique will help determine whether this is residual DMC or thickened soft tissue or bone.

Dermoscopy

Dermoscopy has become central to all dermatological assessments of focal pathology, and this includes periungual changes. There is limited literature on the appearances mostly relating to Type A cysts [3]. However, it is mainly the Types B and C where the clinician needs tools to progress the diagnosis. With gel dermoscopy, any pigment in the longitudinal groove of a Type B cyst can be evaluated, and usually, the irregular brown purple pattern of haem can be discerned (Figs. 3.9 and 3.10). The nature of the keratinous protrusion from beneath the proximal nail fold at the tip of the DMC can also be seen and usually differentiated from a fibroma. The material is often a combination of compacted squames and small amounts of dried exudate arising from the pathology.

The dermoscopic appearance of a Type C cyst is not important in their own right, but the assessment is useful for addressing the differential diagnoses of melanoma, squamous cell carcinoma and glomus tumour.

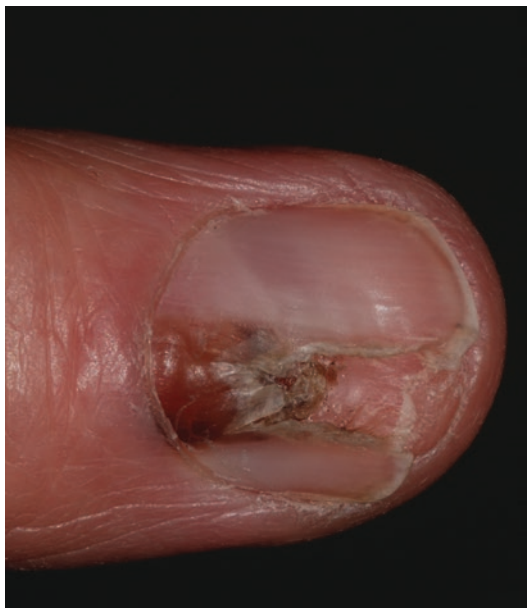

Fig. 3.9 Blood trapped in the longitudinal groove of Type B myxoid can create an impression of longitudinal melanonychia

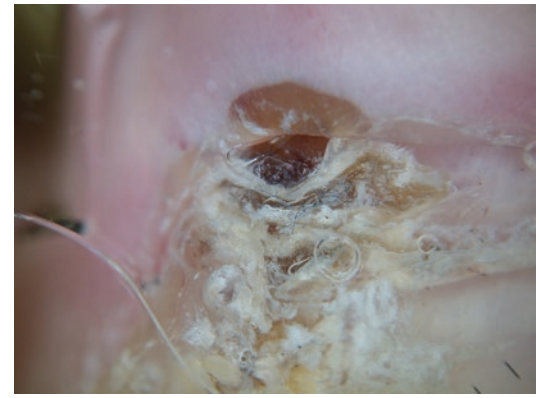

Fig. 3.10 Dermoscopy of blood and origin of Type B myxoid can be helpful

Ultrasound

There is a literature on ultrasound and the nail, and DMC is an ideal pathology to identify with this tool [4]. However, with transillumination, it is rarely needed.

X-ray

An X-ray may reveal osteoarthritis, which is a classic association. In the orthopaedic hand surgery literature, osteophytes associated with DMC have been the focus of surgical treatment. The logic is that the small spurs of bone rub against and erode a hole in the synovial capsule. Their removal is undertaken with bone rongeurs or similar. This approach is effective but with a level of morbidity which may not always be warranted.

MRI

Magnetic resonance imaging of the nail unit is an excellent means of identifying a range of periungual pathologies [2]. It can localise DMCs and sometimes their connection with the joint. If transillumination is positive, it is probably not needed given the expense and lack of additional contribution. However, there are instances where

the diagnosis remains unclear, particularly for Type C DMC, and MRI will help delineate and characterise a range of subungual pathologies such as glomus and acral fibromyxoma as well as DMC, and this may be helpful in treatment planning and consent.

Treatment

No Treatment

Thirty years of treating DMC has shown that it is a fluctuating pathology such that it can resolve or diminish whilst people are awaiting surgical treatment. It is also clear that Type A is rarely harmful in any way, although it is often regarded by patients as ugly or inconvenient. It can also be associated with pain of arthritis arising from the adjacent joint with the consequent expectation that treatment will resolve this. This is rarely the case, and in fact, there may be increased stiffness and discomfort in some instances as effective treatment typically requires some inflammatory process which will result in minor scarring of the synovial capsule to block the leak. Furthermore, all treatments have their relapse rate, and although these vary according to technique, clinician and characteristics of the DMC, it is best to moderate the patient expectation of cure. Eighty per cent cure at 5 years would be a good outcome for those with osteoarthritis where the causal processes will continue to take effect.

This means that for a good number of patients, simple explanation and advice on how to manage rupture is a satisfactory outcome.

Self-Care

Options of self-care are mainly repeated puncture, only possible in Type A cysts. This approach in 40 patients led to a resolution in 72% after two to five treatments, but no follow-up period is given [5]. Where patients are to do this for themselves, it is important to emphasise the need for sterility. There are no reports of infection following puncture alone, but in principle, the pathology communicates with the joint which has risk. The fact that the joint is relatively "high pressure" in comparison with the cyst may reduce this risk. But it is best to advise the patient to use sterile technique. Following rupture, there is a case for applying a compressive dressing to the evacuated cyst. This is to counter the escape of more fluid from the DIPJ and rapid recurrence. If the overlying epidermis and dermis can be encouraged to stick down to the dorsum, then it may help.

Single Visit

Clinical practice differs according to healthcare systems. In some instances, the aim would be to achieve diagnosis, patient education and treatment all in one visit. Where this is the case, the clinician has to choose the single, most deliverable and effective treatment. This is usually a compromise and could be a combination of one of three main options: simple puncture and pressure, puncture and pressure combined with cryosurgery or intralesional sclerosant. All of these are only possible in Type A cysts.

Combination of puncture and pressure is best undertaken with a size 11 scalpel with formal sterile technique. Some patients and clinicians may prefer local anaesthetic, but often, it is not needed if done quickly and on more superficial lesions. The procedure may be a means of demonstrating how to repeat the process for themselves and hence the benefit of not using local anaesthetic.

Adding cryosurgery to the treatment increases efficacy. Cryosurgery with a double 30 s freeze-thaw cycle is reported as effective in over 80% of patients. However, this is likely to create a scarred nail fold and considerable morbidity [6]. The common practice is to treat with a double 10–20 s freeze-thaw cycle. This results in cure in about 50% of patients, requires an anaesthetic and has only moderate post-operative morbidity.

The literature on sclerosant suggests it is a convenient and effective treatment. However, it can result in considerable soreness for some patients and some surface scarring.

Serial Visits

If it is possible for the patient to return for serial treatments, a 3-month interval allows for assessment and retreatment in a time frame that appears to increase the chances of success for all the three modalities that might otherwise be used as single treatments. Both cryosurgery and sclerotherapy [7, 8] can consolidate their benefits if repeated at intervals.

Surgery

Surgery shares principles with many other repair procedures where something is leaking. The approaches include the following:

1. Identifying the cause
2. Resolving the cause
3. Removing the effect
4. Patching up the defect which gives rise to the effect

These principles can be applied to hernia repairs, leakage of cerebrospinal fluid or a leaky domestic pipe. In the context of treatment of myxoid cyst, the aim is to maximise the efficacy whilst minimising the morbidity, whilst keeping in mind the cost and ease of delivery.

Identifying and resolving the cause entails establishing the bone spurs or irregularities associated with osteoarthritis and establishing the point of leakage of the synovial capsule. The former can be done with imaging – usually X-ray. The latter can be highlighted by MRI, but it is more practical to do it whilst operating by the injection of methylene blue dye into the joint via the volar surface and then to track its escape into the myxoid cyst. Both features of the cause can be treated surgically, with the removal of the abnormal bone with rongeurs [1] and the ligature of the path of synovial escape with absorbable suture [9]. Addition to the direct effects of these interventions is the indirect provocation of inflammation and scarring, and this probably contributes to the "patch" of scar tissue, which then acts as repair of the leak. Some treatments, surgical, sclerosant, cryosurgery or laser, probably primarily act through inflammation and secondary "patching" by scar. Even the repeated puncture and evacuation as self-care is likely to result in scarring.

The choice of procedure depends on patient, clinician, lesion and circumstances. The variety of options is greatest for Type A lesions. Types B and C require preliminary surgery to gain access to the myxoid cyst. Simply reflecting the nail fold to see the origin of a Type B myxoid creates sufficient inflammation when combined with light curettage and cautery to cure the problem in many instances [10]. The same is true of a subungual myxoid, where gaining access requires the removal of the nail and incising the matrix or nail bed and further dissection to get to the origin of the leak proximally. When access, drainage, light curettage and cautery are combined with moderate post-operative compression and immobilisation for 2 weeks, cure can be expected in about 70% of patients for the next 5 years [11].

Table 3.2 outlines the steps for treatment of Type A myxoid. Elements can be modified or omitted according to the circumstances.

Other Modalities

Laser

Short case series using CO_2 laser suggest that it can be an effective treatment for myxoid cysts, but it is rarely used.

Table 3.2 Approach to management of myxoid cysts

	Treatment step	Intervention	Comment
1.	Identify the origin of the leak	X-ray	May require two views to identify relevant osteophytes
		MRI	Good for identifying all relevant anatomical elements
		Methylene blue	Requires some skill and only a small amount should be injected (see references)
		Transillumination	Good general guide to the subclinical extent of the synovial leak and likely origin
		Direct visualisation	Sometimes possible at surgery, but usually subjective and open to error if no marker dye
2.	Address cause of the leak		
	All require a flap to be raised for direct view	Remove osteophytes with bone spurs	Effective but liable to post-operative morbidity. Best done by those used to working within the joint
		Ligature path of escape of synovial fluid	Easy when path highlighted by methylene blue. Approximate when not. Avoid pro-inflammatory sutures if joint already sore
		Gentle curettage and cautery of the source of leak and surrounding area	Good option and works best when combined with raising a flap, which also minimises morbidity but localises scarring to the area of leaking capsule
3	Promote healing with compacted scar	Post-operative partial immobilisation with firm dressing. 2 weeks	
		Ensure gradual mobilisation thereafter to prevent stiffness and loss of function	
4	Promote non-specific scarring	Repeated sterile puncture and drainage	Can be delegated to a patient in some instances
		Puncture and drainage combined with cryosurgery	Increased morbidity and may require local anaesthetic, especially with longer freezes
		Laser	CO_2 laser can be effective as a more precise version of liquid nitrogen
		Injection of sclerosant	Comparable to cryosurgery and can result in substantial inflammation
		Puncture and drainage combined with curettage	Caution with respect to depth of curettage and damage to underlying structures

Sclerosant

Sclerosant suitable for vascular sclerotherapy has been reported by several authors. The outcomes are generally good. It may require serial treatments in those only partially responding at the outset. The downside is the level of inflammation that can arise, and this is a trade-off in all the more effective treatments where inflammation is likely to be part of the mechanism whereby scar tissue occludes the leak from the synovial capsule.

Esson [7] reported success in 84% in a case series of 63 patients where up to three treatments were provided with polidocanol solution (hydroxy polyethoxydodecane – Aethoxysklerol), which is a form of detergent. There was no sig-

nificant longer-term follow-up, although a smaller series reported it in about 10% of those who had initially responded when followed over 18 months [8].

Special Scenarios

Fingers Versus Toes

People present more commonly with DMC of the finger than of the toe [7], although we do not know if this is a fair indication of prevalence. The complaints and challenges are different. Those in the finger often cause disquiet concerning the appearance, with less concern over function. Toe DMCs are troublesome because of rubbing on footwear and can be slow to heal if they burst. The literature on management largely pertains to fingers, but the same techniques can be used on toes. However, the success rate is about 30%–50% lower. One explanation for this might be the pressure gradient across the synovial capsule. In a finger, the movement will act to compress the content of the joint by some small amount. In a toe, the same pressure change is supplemented by the additional pressure due to the position of the toe at the end of a column of fluid – the human body. With walking, there is a further force arising with the impact of the proximal foot on the distal point of contact with the ground. The latter will be stationary, and the former will have momentum carrying it forward. This momentum will be dissipated in the structures of the foot. And if there is a weakness in the synovial capsule, the force may cause it to rupture.

Multiple Lesions

Where myxoid cysts are associated with a generalised cause such as osteoarthritis, they are often multiple. This may not always be apparent at presentation, but be evidenced over time. The other evidence is with transillumination of all the digits one at a time. It is not uncommon in an elderly person with osteoarthritis to find small DMCs in other digits which are not clinically apparent. In the limited literature on multiple DMCs, the cause was occupational in someone undertaking a manual job which caused them to repetitively flex and strain the DIPJ with consequent DMCs in most fingers [12].

Recurrent Lesions

Recurrence is in two patterns. For many types of treatment, relapse is expected in a large number, with the expectation that the DMC will be smaller and continue to dwindle with serial treatments. This is the case for repeated puncture and puncture with cryosurgery or sclerosant therapy. Most surgical treatments aim to be definitive, but when they aren't, the relapse can occur over a long period. For larger DMCs, located directly over the joint, relapse can be almost immediate. Others are typically over years. Re-operating with the same procedure on the first group may continue to fail, in contrast to the second group which can be provided with a further few years of relief. Where DMCs are resistant to the surgical approaches of the dermatological surgeon, the orthopaedic surgeon may have some options. These can include a range of procedures that promote drainage and fibrosis of the joint with consequent rigidity.

Complications of Treatment

Infection, pain, stiffness, slow healing, loss of function, altered sensation and recurrence are the main adverse outcomes of treatment and, in particular, surgery (Table 3.3). Infection has particular significance because of the potential communication with the joint space. Purulent infection of the joint space is extremely painful and carries the risk of osteomyelitis, tendon rupture and potential loss of the tip of the digit. Surgeons undertaking DMC procedures should carefully consider the indication for antibiotic prophylaxis.

Pain is rarely marked but varies according to the nature of the treatment. For the surgical procedures, it is usually moderate and requiring only elevation, paracetamol or NSAIDs for the first 48 h, with an emphasis on the dose before bedtime. If pain increases at 48–72 h, it can be an early clue to infection and requires assessment.

Table 3.3 Complications of treatment of myxoid cyst

Complication	Factors and clues	Action
Infection	Rare More likely with surgery and risk factors of patient and site (toe > finger) Indicated by increased pain at >48 h Risk of osteomyelitis and infective arthritis	Ensure clear patient information and examination at 48–72 h Low threshold for antibiotic prophylaxis where risk factors pertain
Pain	Surgery usually only modest short-term pain Inflammatory treatments can be more uncomfortable, e.g. cryosurgery or sclerotherapy Regional pain syndrome (reflex sympathetic dystrophy), a rare complication of all-digit surgery and to be kept in mind	48 h of paracetamol +/− NSAIDs and elevation normally sufficient If pain >48 h, ensure clinical review
Stiffness	Most treatments have stiffness as an expected side effect inherent in treatment Gentle mobilisation after 2 weeks is normal	Excess mobilisation or the lack of rest early may dispose of relapse/treatment failure
Slow healing	Rarely a problem for fingers Inflammatory treatments may take longer to heal than surgical treatments Problems more likely with any treatment delivered to toes	Recommend risk assessment for all surgery and in particular toe surgery in those >60 years
Loss of function	Longer-term loss very uncommon with dermatological treatment Orthopaedic treatments may be designed to fix the joint and hence reduce function as a trade-off Tendon rupture can arise secondary to intense inflammation or infection with loss of extension	If there is loss of function, recommend addressing the problem as part of a multidisciplinary team with hand surgeon and physiotherapy
Altered sensation	Very common in post-operative period of surgery May be in part connected with nature and duration of surgical tourniquet Medium-term (up to 6 months) altered tactile sensation	Common to arise, but rarely a problem with suitable patient warning

For cryosurgery and possibly sclerotherapy, the inflammation that arises can cause substantial pain and need managing in the same way as a skin burn. With healing from all treatments, there may be some increase of stiffness, partly through the period of post-treatment immobilisation and partly through the additional scar tissue created as part of treatment. Usually, this is amenable to gentle mobilisation over the following weeks whilst keeping in mind that use of the joint creates an increase in pressure and likelihood of rupture of any repair.

Slow healing is usually a complication of treatments relying on scarring through inflammation as the means of cure, such as cryosurgery and sclerotherapy. Flaps and surgical treatments are normally settled within 2 weeks. However, as a disease of the second half of life, it is also associated with diseases of that era which can complicate healing, in particular, peripheral vascular disease, diabetes and Raynaud's disease. All digit procedures, particularly those on toes, should be undertaken with caution in such people, and it is prudent to obtain the arterial brachial pressure index (measured by a continuous-wave Doppler ultrasound) of the feet for all people over the age of 60.

Loss of function is rare with any of the treatments outlined above. Some degree of loss of function can arise if there is direct surgery on the joint, such as with osteophyte removal. In more extreme solutions offered through orthopaedics, joint fixation can be intentional and the outcome of a calculated risk-benefit discussion. Rupture of the extensor tendon can be secondary to infection or direct inflammatory response, where some element of infection is difficult to determine.

Altered sensation is common after all-digit surgery. It is particularly of the digit pulp and may reflect the duration of tourniquet application, or its tightness should one be applied. It is not clear if this is due to direct pressure on the digital nerves with subsequent neuritis or whether the swelling of the tip of the digit is the cause. Anecdote suggests that altered sensation is less where a tourniquet is avoided and a bloodless field is achieved through the use of epinephrine in the digit block anaesthetic. Where altered sensation arises, it is usually limited to the detection of texture and surface type rather than being a loss of perception. In most instances, it resolves within 6 months. Where there has been substantial post-treatment inflammation and pain, there is a small risk of regional pain syndrome, previously known as reflex sympathetic dystrophy. It features include altered tactile sensation as well as disproportionate pain. This should be treated promptly and actively given that it becomes more difficult to treat over time if allowed to fully establish.

Recurrence of DMC is common with all treatments over the long term. The common scenario is one where there is a damaged ageing structure (the synovial capsule) wrapped around a joint with progressive bony changes (the osteoarthritic joint with osteophytes). The moderating factor is that if it is accepted that pressure within the joint is a factor and activity causes pressure, activity decreases with age and so the pressure on the ageing fabric of the joint tends to reduce over time. Whilst this is conjecture, it is consistent with the observations that peaks of activity cause exacerbation of DMC and, equally, their prevalence does not appear to increase in tandem with increasing manifestations of osteoarthritis and age.

Atypical Ganglia

Atypical ganglia can be described as those not initially recognised as such. This is a function of the experience of the clinician. For some, all variants other than a type A may be atypical, and it remains common amongst dermatologists to diagnose Type B as a fibroma and Type C as a sinister anonymous mass. Transillumination should be remembered as a simple tool for resolving this at the first consultation and should be used on all periungual and subungual masses.

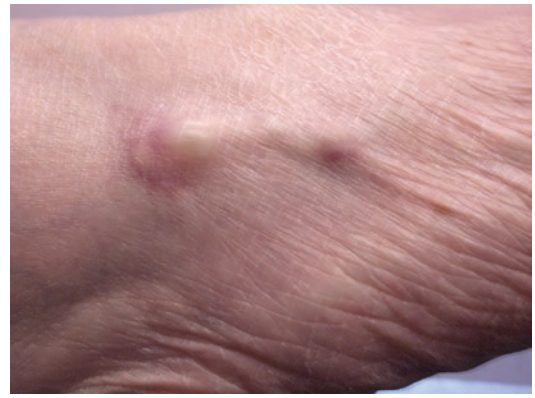

Fig. 3.11 Myxoid cysts are ganglia and can arise in a range of locations, such as here on the dorsolateral aspect of the foot

Where blood is trapped in the nail plate and dried myxoid matrix, it can present an appearance confused for melanonychia (Fig. 3.9). Volar lesions or those of the ankle (Fig. 3.11) or knee can also be misleading. In all of these, transillumination and a careful history to elicit the common feature of "gel-like" discharge provide the diagnosis.

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4 Advances in MRI of Glomus Tumors of the Fingertips

Jean-Luc Drapé

Because of their highly characteristic clinical symptoms, glomus tumors are probably the best-known nails tumors. Glomus tumor is a benign and vascular hamartoma that originates from the neuromyoarterial cells of the glomus bodies (Masson's glomus) in the reticular dermis, most often at the nail bed. Many recent studies have provided refinements in imaging features and imaging strategies.

Clinical Exam

Glomus tumors occur more frequently in women between 30 and 50 years old. Clinical diagnosis is based on the classic triad of cold hypersensitivity, pinpoint tenderness (Love's test), and paroxysmal pain. The pain can radiate up to the elbow or even the shoulder. A tourniquet at the base of the finger or a blood pressure cuff inflated to 300 mm Hg is able to alleviate the pain. Cold hypersensitivity is not the rule and noted between 31% and 42% of the patients [1, 2]. Some rare painless cases are reported [3]. A bluish or violaceous spot of the lunula or the nail bed and a reddish line extending distally may be present in 43% of cases (Fig. 4.1) [4]. The nail may be slightly elevated over the lesion or even split. The classic subungual location seems lower (55%) than that previously published (75%–90%) [2, 5]. Rare cases of glomus tumor originating directly from a digital nerve are reported [6, 7]. Infection on a ruptured tumor is exceptional [8]. Physical examination and medical history may be informative enough for a correct diagnosis. However, the mean delay for the diagnosis needs usually several years. Histology consists of a convoluted

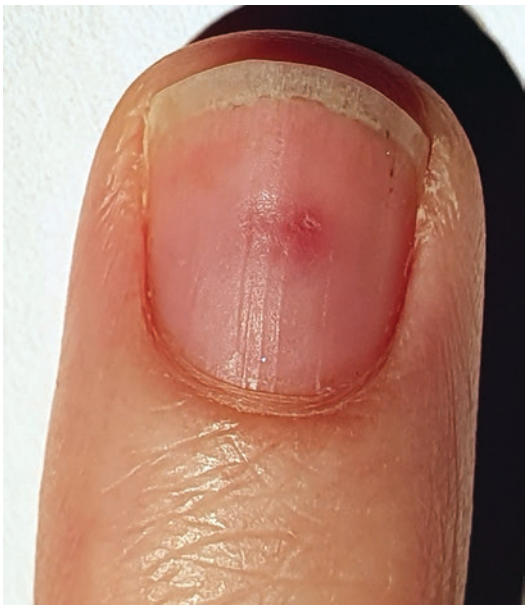

Fig. 4.1 Reddish spot at the midline of the nail bed of the fourth finger of a 38-year-old female

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arteriovenous anastomosis with a relative paucity of a vascular lumen surrounded by a thick layer of modified smooth muscle cells and nerve elements. Surgical excision is the most effective treatment.

MRI

The role of imaging during the management of a glomus tumor is poorly helpful for visible lesions with characteristics symptoms [2]. Radiographs present a low sensitivity and specificity with bone erosion of the dorsal cortex of the distal phalanx in 36% of cases [9]. Ultrasound can detect tumors as small as 2 mm but remains strongly dependent on the expertise of the operator (but as well as for MRI).

These last year's numerous studies assessed not only the accuracy but also the insufficiencies of MRI to diagnose subungual glomus tumors. MRI is useful when the location of the tumor is in doubt or in the case of suspected multifocal lesions [10].

MRI is more accurate than plain films to depict associated bone erosion of the distal phalanx. Usually, the lesion is well defined with sometimes a pseudocapsule. The signal is homogeneous iso or slightly intense on T1 WI, highly intense on T2 WI, and highly enhanced after intravenous injection of gadolinium (Fig. 4.2). However, in some cases, the

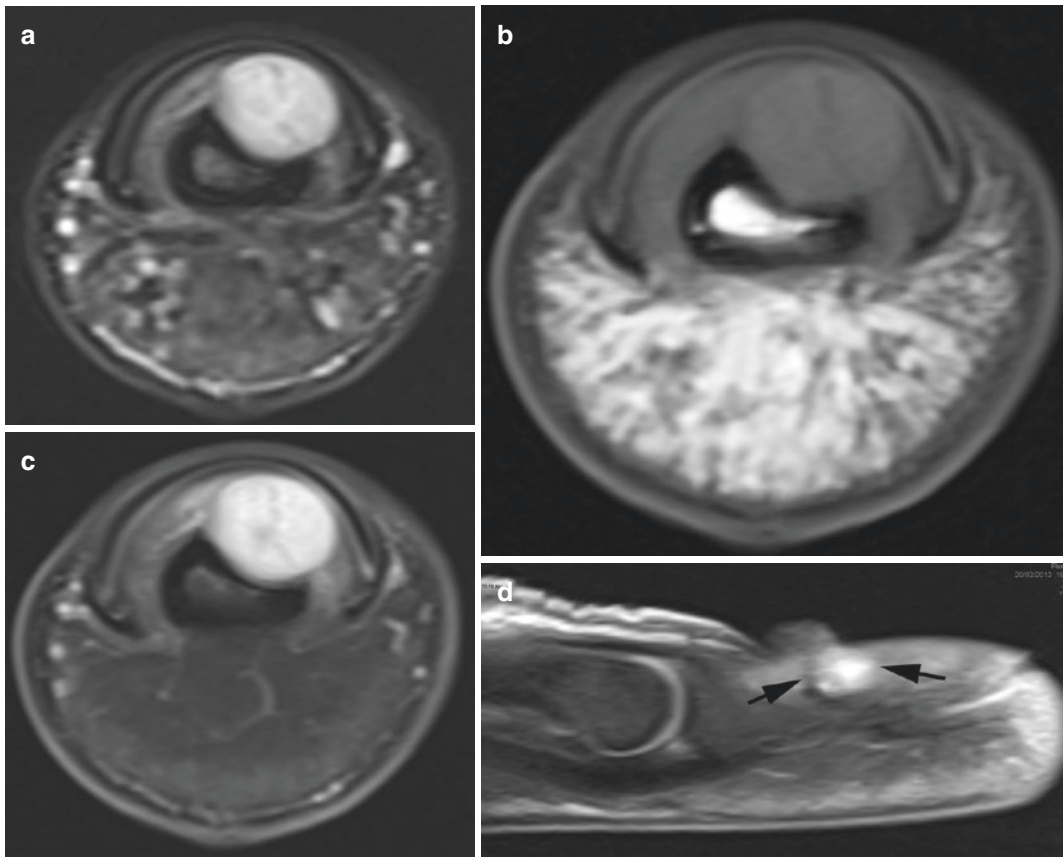

Fig. 4.2 Typical glomus tumor of the left third finger of a 32-year-old female. (**a**) Axial T2 fat-sat WI, (**b**) axial T1 WI, (**c**) axial, and (**d**) sagittal T1 fat-sat WI after intravenous injection of gadolinium. Typical patterns with well-defined limits and ahigh contrast between the glomus tumor and the dermis of the nail bed: high signal on T2 WI, slightly high signal on T1 WI, and strong enhancement. Deep bone erosion of the dorsal cortex of the distal phalanx. The tumor (arrows) is distal to the matrix on the sagittal slice

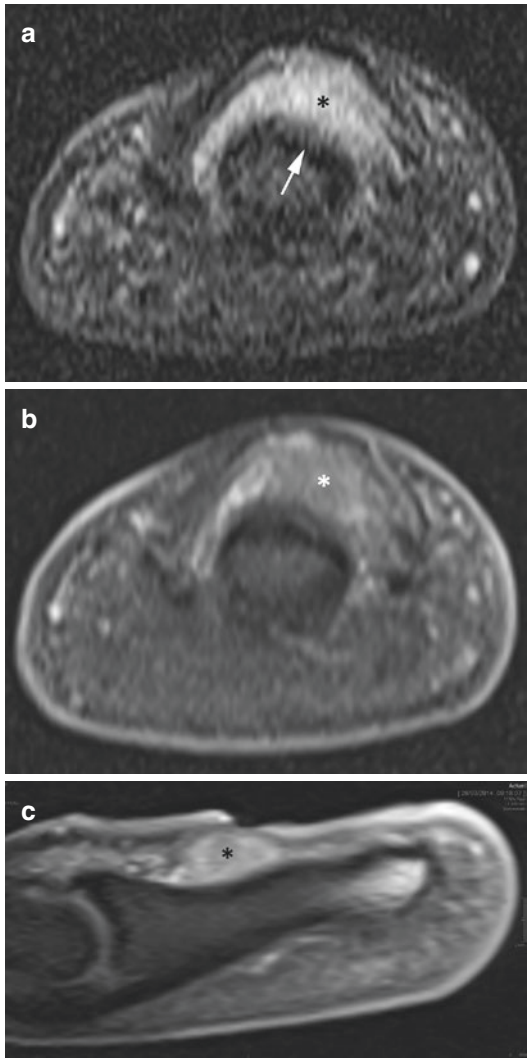

Fig. 4.3 Atypical glomus tumor of the right fifth finger of a 42-year-old female with slight enhancement. (**a**) Axial STIR and axial (**b**) and sagittal (**c**) T1 WI after intravenous injection of gadolinium. The tumor is difficult to highlight with a signal close to the signal of the surrounding submatrical dermis. Indirect signs are the dorsal shift of the matrix and the superficial bone erosion of the dorsal cortex of the phalanx (arrow)

degree of enhancement on T1 post-contrast imaging may be mild to moderate, remaining isointense to the surrounding enhanced nail bed (Fig. 4.3). The PPV of MRI is high 97% in the diagnosis of glomus tumors as small as 2 mm among 42 patients [11] and 100% among 21 patients [12]. However, MRI presents a low specificity and low NPV: a negative image does not rule out a glomus tumor [1, 12]. Among all patients, 10% have a nondiagnostic MRI [11]. Technical insufficiencies of MRI (misfit coil or protocol, too low spatial resolution) may explain these negative exams. This may be also due to the lack of detection of the smallest tumors on MRI, and surgical exploration may be performed despite a negative MRI. Over time, tiny glomus tumors may become visible and detectable with a delayed MRI (Figs. 4.4 and 4.5). In solid glomus tumors with relatively low vascular lumens, the signal may be similar to the surrounding tissue and can be more difficult to detect (Fig. 4.3). Some lateral location may be difficult to detect on MRI (Figs. 4.5 and 4.6). Submatrical dermis usually presents a high vascularization and may occult a glomus tumor in his area (Fig. 4.7). Performances of MRI may be improved with enhancement curve and/or MR angiography showing an early and partial enhancement at the arterial phase with a progressive and complete enhancement on more delayed acquisitions (Figs. 4.8 and 4.9). A delayed washout of the glomus tumor is possible (Fig. 4.10). On the other hand, potential lesions that exhibit focal high signal only on T2 sequences but without correlative findings on other sequences are more likely to be false positives (Fig. 4.11) [13].

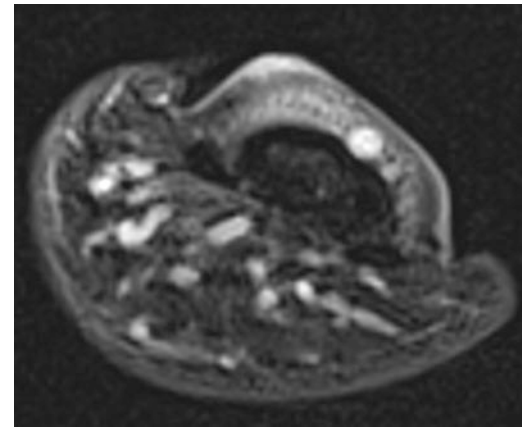

Fig. 4.4 Tiny glomus tumor of the right thumb of a 57-year-old female. Axial T2 fat-sat WI with a 1.3-mm large tumor in the deep dermis of the nail bed lying of the dorsal cortex of the phalanx. A high spatial resolution is necessary to depict such a small lesion

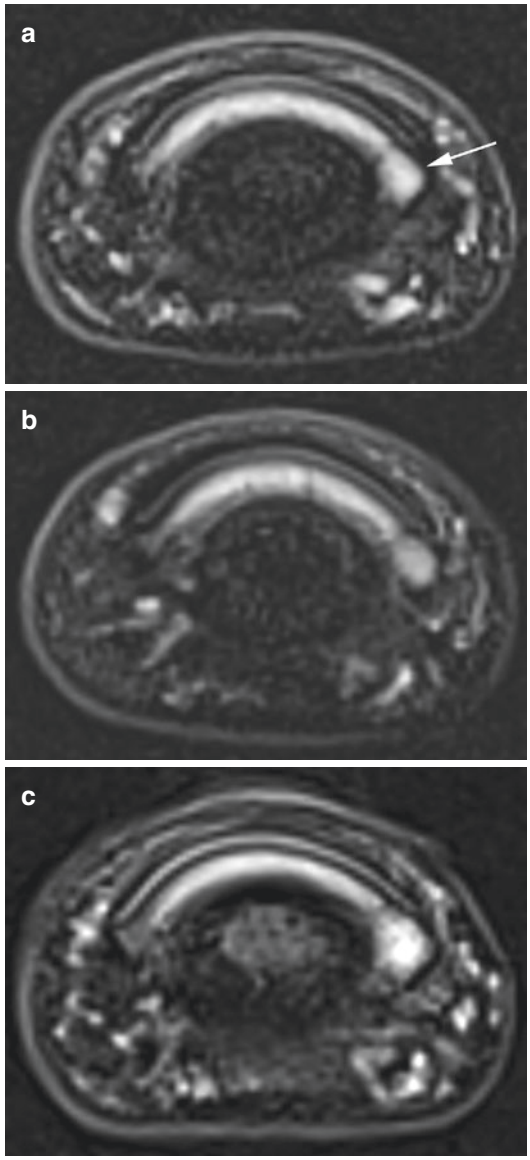

Fig. 4.5 Follow-up of a tiny glomus tumor of the left finger of a 26-year-old male. Axial T2 fat-sat WI in (**a**) 2014, (**b**) 2015, and (**c**) 2019. The tumor is located in the lateral part of the nail bed close to the rima ungalum. The initial size of the tumor was 1.5 mm and reached 2.5 mm 5 years later

However, in more complicated scenarios like suspicion of recurrence after surgery, the predictive power of the clinical exam declines, and the usefulness of MRI increases. In these cases, MRI provides a greater sensitivity than the clinical exam but need a perfect technical protocol with MR angiography. An associated Raynaud's syndrome or vasculitis may disturb the quality of MR angiography (Fig. 4.12). A warm bath of the hands a few minutes before the exam can improve the dynamic injection of chelate of gadolinium.

Glomangioma

Glomus tumors are commonly solitary subungual lesions of the nail bed. Histopathologically, based on the predominant tissue type present, glomus tumors are classified as solid glomus tumors, glomangiomas, or glomangiomyomas. Vascular forms of glomus tumors or glomangiomas (10%–25% of glomus tumors) have a different clinical presentation and are usually multifocal, bluish, painless, and extradigital [14]. Roughly 10% of glomus tumors are multiple, which may be the cause for presumed recurrence (Fig. 4.13). Glomangiomas in subungual location are rare and do not often show the classic triad of symptoms associated with glomus tumors [15]. They can extend to the periungual skin. They can often be misdiagnosed as vascular malformations, resulting in delayed diagnosis and inappropriate treatment. Histological examination is necessary to rule out a clinically indistinguishable benign or malignant melanocytic tumor (blue nevi or melanomas), a venous malformation, or a blue rubber bleb angiomatosis [14]. Glomangiomas are distinguished from solid glomus tumors by the predominant vascular component and less defined limits.

Glomus Tumors and Neurofibromatosis Type 1

Glomus tumors have recently been reported in individuals with neurofibromatosis type 1 (NF1) [4]. They frequently appear as bluish

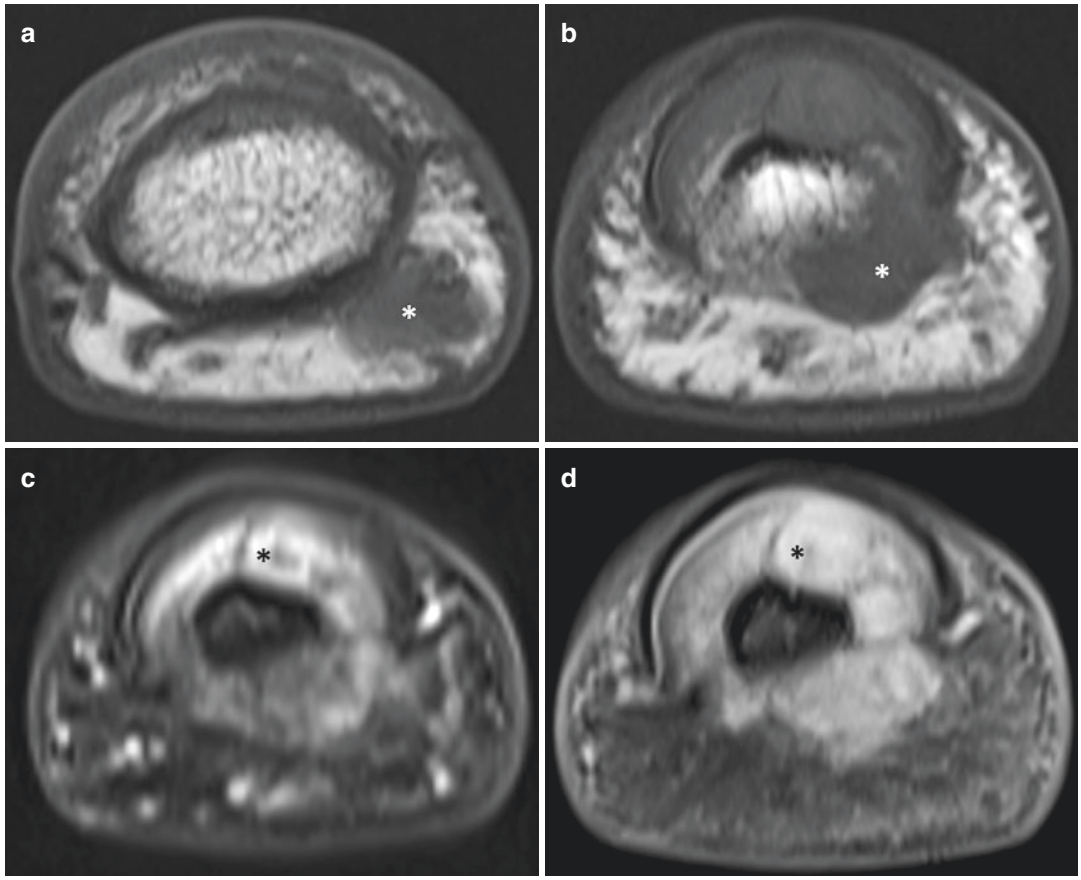

Fig. 4.6 Ill-defined glomus tumor of the midlateral nail bed with extension to the pulp of the right thumb of a 44-year-old female. (**a**, **b**) Axial T1 WI: the tumor extension to the pulp (*) is highlighted by the surrounding fatty tissue. (**c**) Axial T2 WI and (**d**) T1 fat-sat after intravenous injection of gadolinium: the tumor invasion extends to the midline of the nail bed (*)

subcutaneous nodules on the trunk and limbs and can be multifocal [13]. Multifocal tumors (16.7%) and tumor recurrence (33.3%) are more common in association with NF1 than in sporadic cases. There is no correlation between café-au-lait macule burden and the number of neurofibromas with the development of glomus tumors. NF1-associated glomus tumors exhibit no neurofibromin immunoreactivity, whereas their sporadic counterparts retained neurofibromin expression. Detection of glomus tumors and particularly multiple glomus tumors should raise suspicion for a concurrent diagnosis of NF1 (Fig. 4.14).

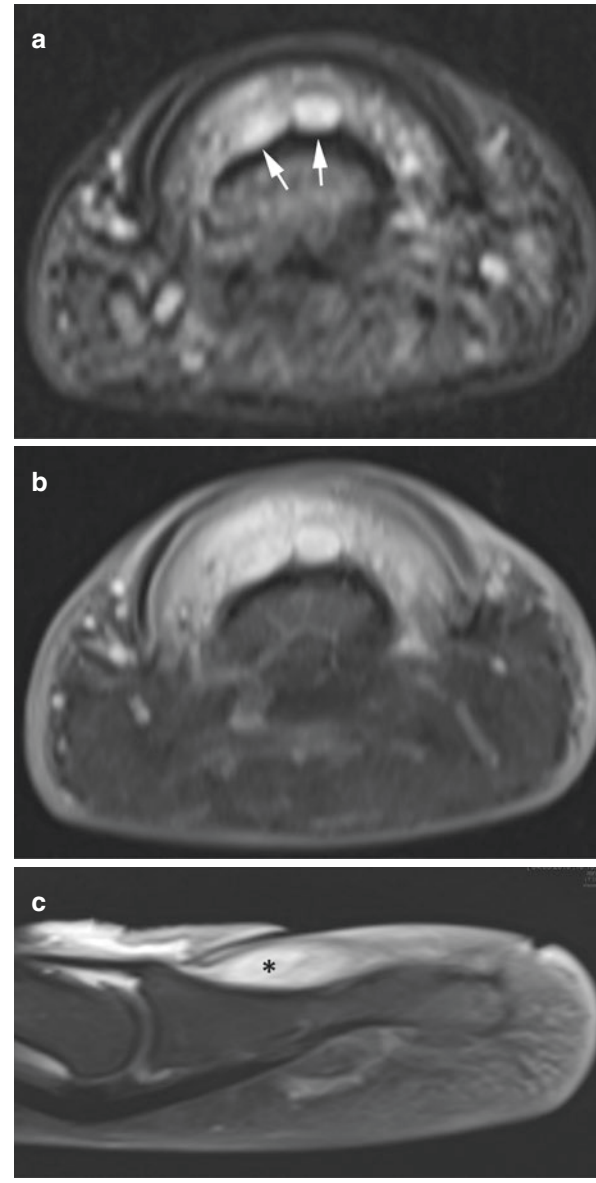

Fig. 4.7 Glomus tumor in the submatrical dermis of the right fourth finger of a 75-year-old female. (**a**) Axial STIR, (**b**) axial, and (**c**) sagittal T1 fat-sat WI after intravenous injection of gadolinium: the bilobulated glomus tumor (arrows, *) is faintly visible due to the high signal of the surrounding submatrical dermis

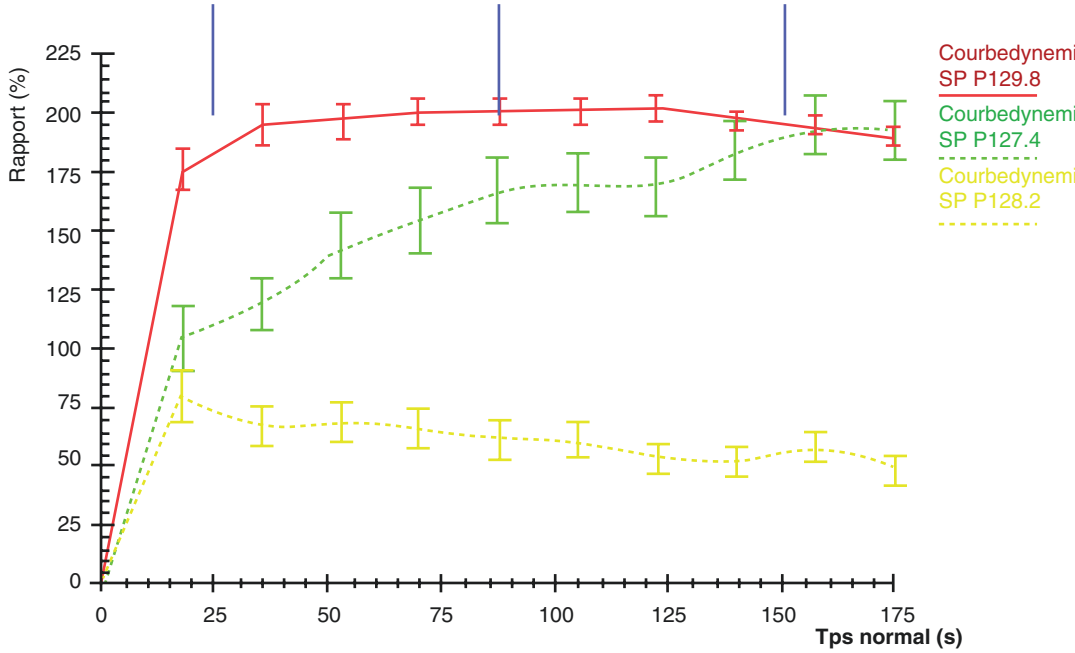

Fig. 4.8 Dynamic enhancement curve of signal after intravenous injection of gadolinium. Red: arterial curve, green: glomus tumor curve, yellow: dermis curve. The glomus tumor presents an early and fast enhancement at the arterial phase and more progressive enhancement on the delayed phase

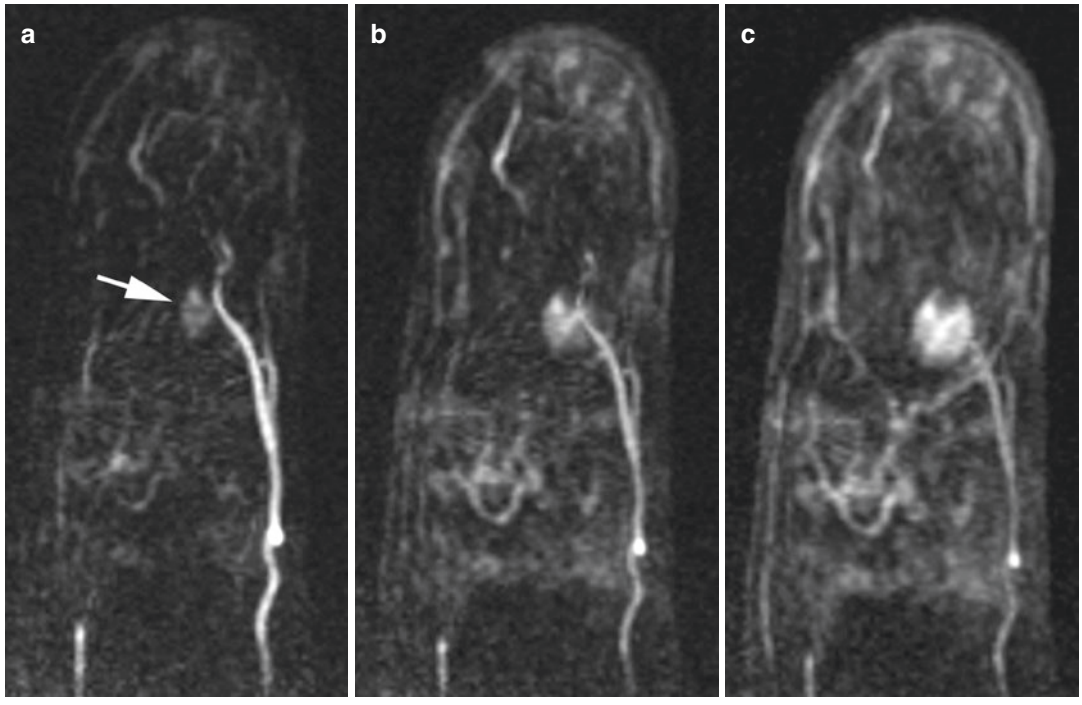

Fig. 4.9 MR angiography of a glomus tumor of the right fourth finger of a 41-year-old female. (**a**) Arterial phase with a dominant radial digital artery and early enhancement of the tumor. Progressive enhancement on the more delayed phases (**b**, **c**)

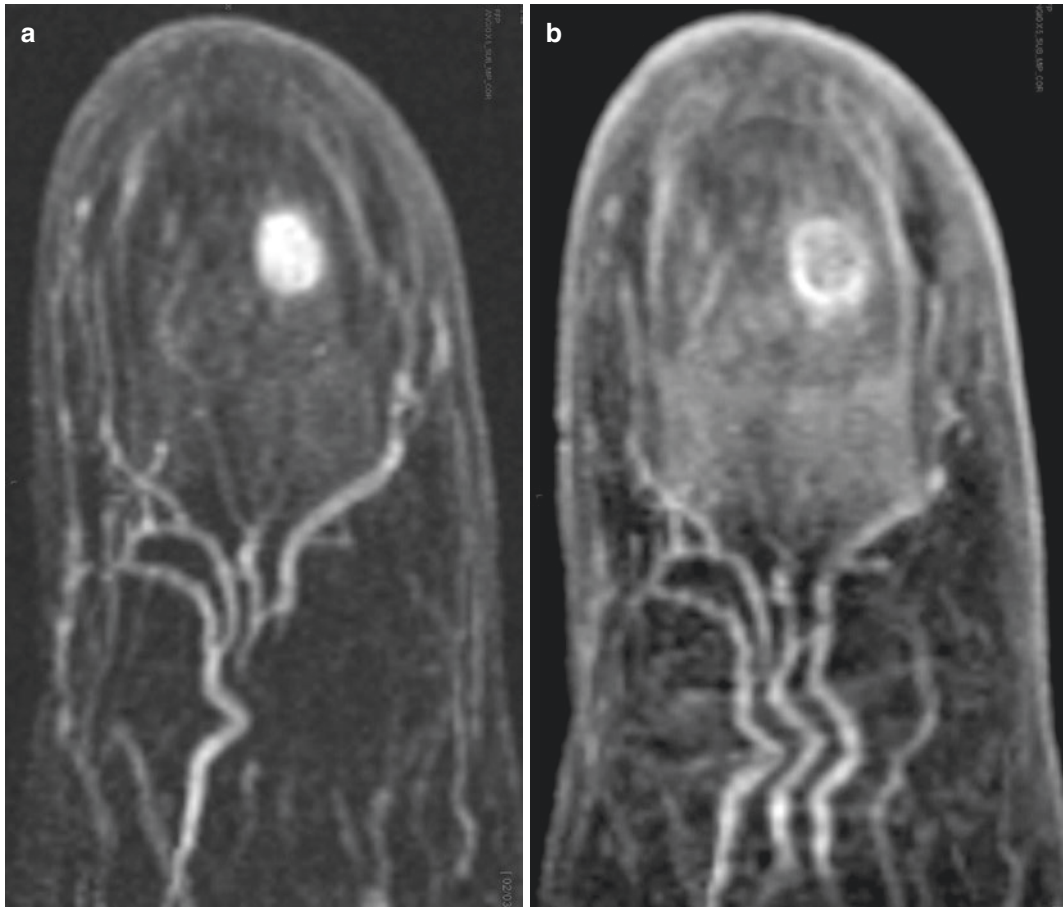

Fig. 4.10 Glomus tumor of the third finger of a 63-year-old female. MR angiography at the (**a**) arterial phase and (**b**) a delayed phase: early and strong enhancement of the tumor. Note the washout of the central part of the tumor on the delayed phase

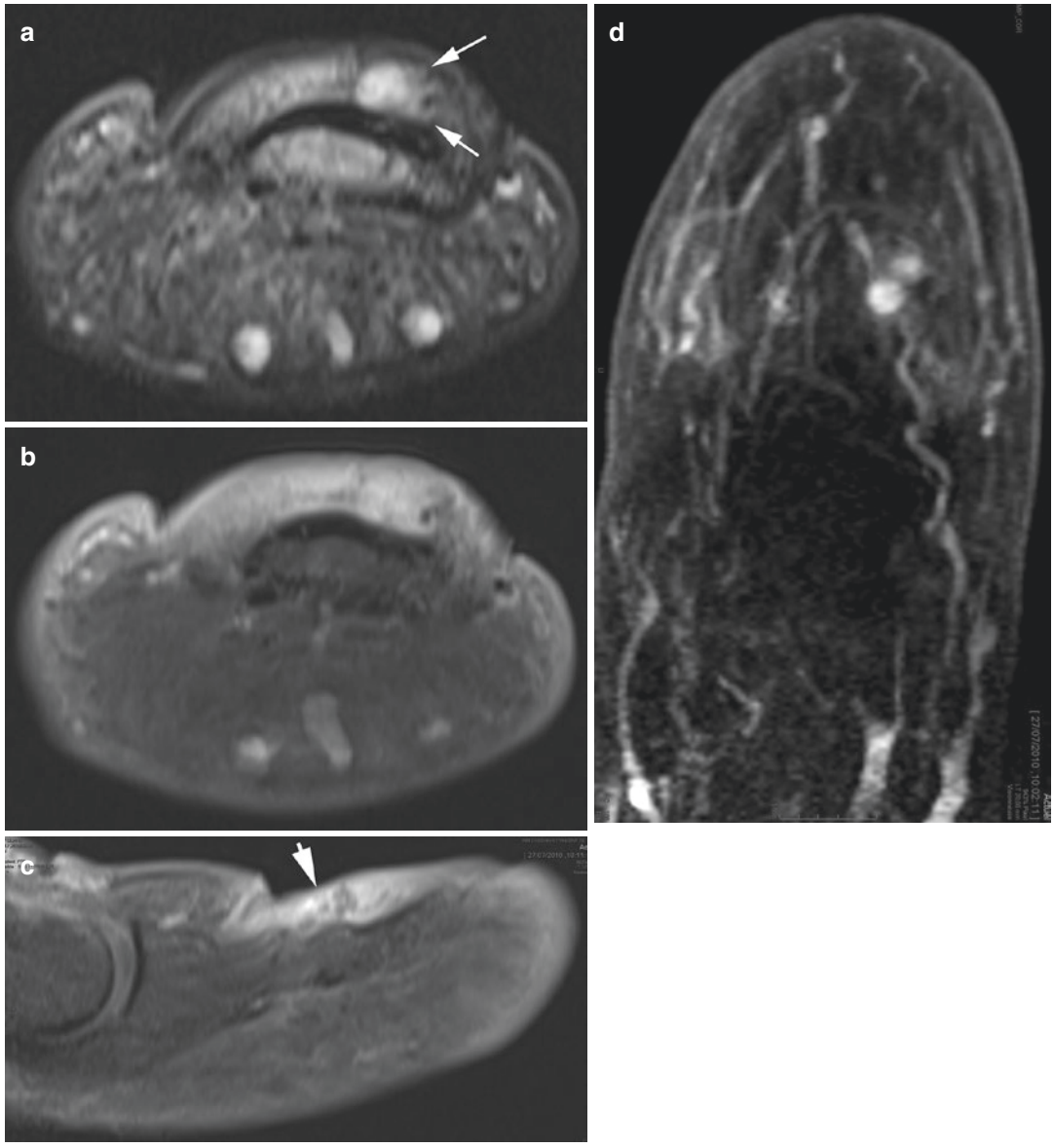

Fig. 4.11 Recurrent glomus tumor of the right thumb of a 63-year-old female. Surgery 5 years before. Recurrent pain after a 6-month free period. (**a**) Axial T2 fat-sat, (**b**) axial, and sagittal (**c**) T1 fat-sat after intravenous injection of gadolinium: the tumor is barely visible with ill-defined limits and postoperative artifacts (arrows). (**d**) MR angiography shows in fact two well-defined contiguous recurrent tumors

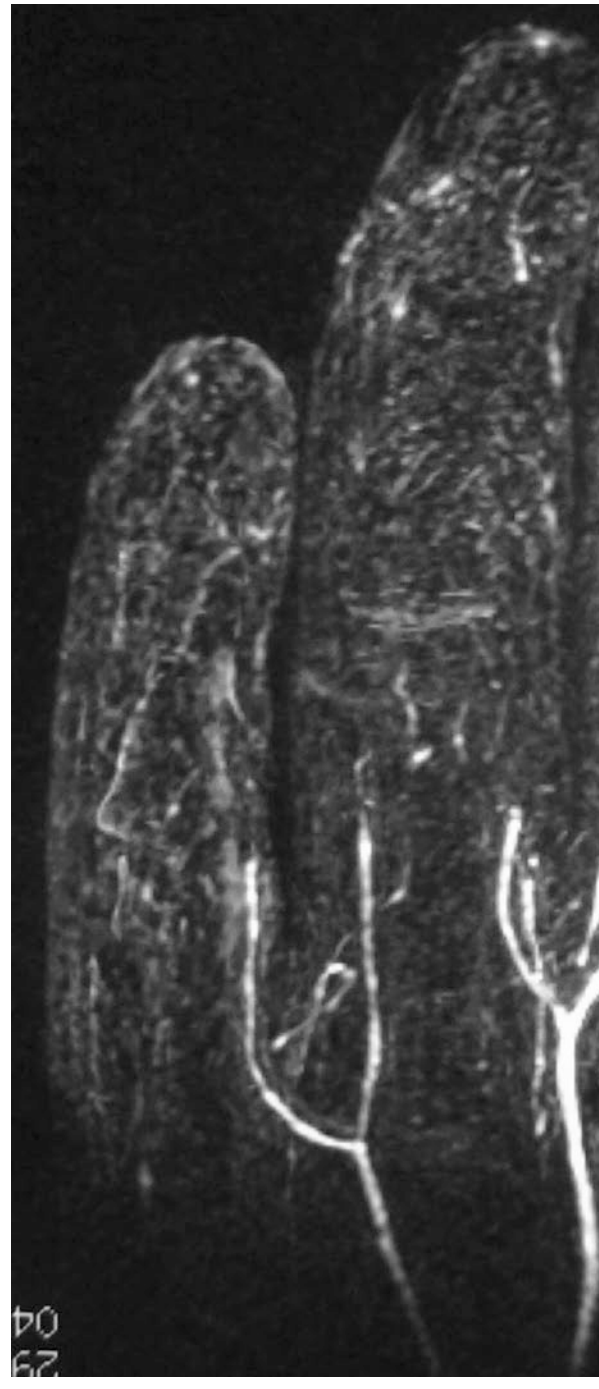

Fig. 4.12 Raynaud's syndrome with a lack of visibility of the vascularization of the fingertips of the fourth and fifth fingers. Note the interrupted thin proximal digital arteries. The detection of the glomus tumor is not possible with MR angiography in this condition

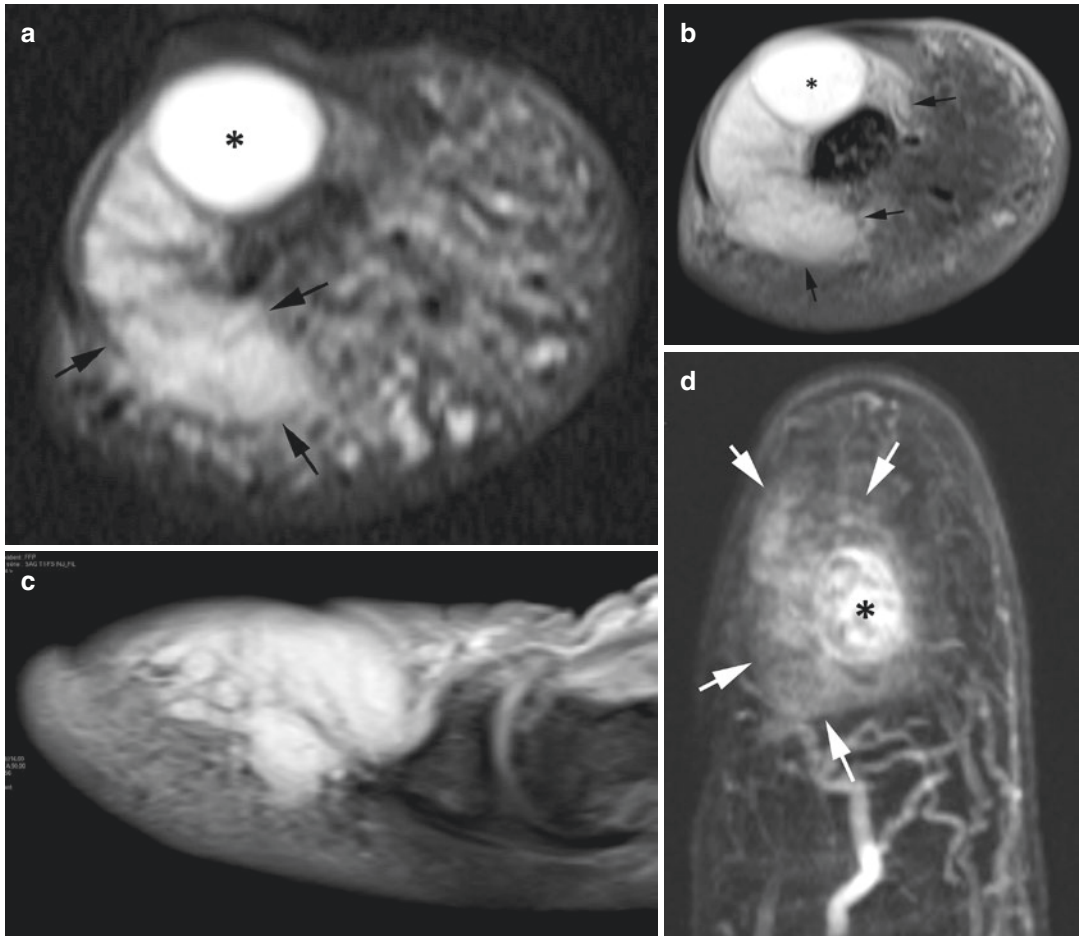

Fig. 4.13 Glomangioma of the left thumb of a 37-year-old female. (**a**) Axial STIR, (**b**) axial, and (**c**) sagittal T1 WI after intravenous injection of gadolinium show an atypical glomus tumor with a round well-defined highly vascularized mass (*) on the midline of the nail bed and infiltrative expansion in the radial part of the nail bed and the pulp (arrows). (**d**) MR angiography better shows these two components of the tumor

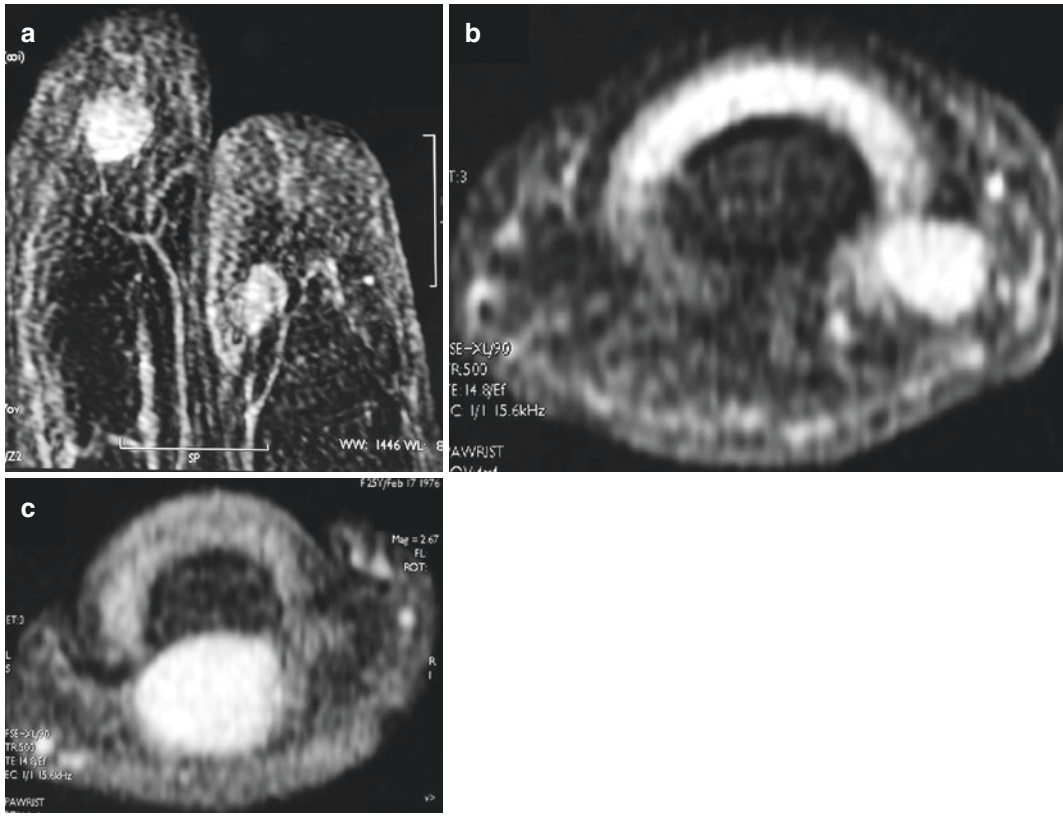

Fig. 4.14 Multiple glomus tumors of the second and third fingers of a 25-year-old female associated with NF1. (**a**) MR angiography shows one glomus tumor on both fingers. Axial STIR (**b**) of the second finger and (**c**) axial T1 fat-sat after intravenous injection of gadolinium of the third (**b**) finger highlight rare locations in the pulp for both fingers

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Trachyonychia

5

Mohamed EL-Komy

Introduction

In 1977, *Hazelrigg* et al. [1] described six children with an acquired nail dystrophy characterized by excessive longitudinal striations and loss of nail luster. They termed the condition twenty-nail dystrophy (TND) and suggested it to be an idiopathic self-limited abnormality that resolves slowly with age [1]. Earlier, *Alkiewicz* in 1950 used the term "trachyonchie" to describe roughness and grayish opacity of nails that consequently develop brittleness with terminal splitting [2]. The two terms TND and trachyonychia had been used interchangeably by dermatologists for decades. Several authors advocate that the term TND has no specific significance or specificity and should be abandoned [3–5]. Trachyonychia meaning rough nails seems to be a better descriptive term for the clinical picture of the affected nails [6, 7]. Confusingly, some authors consider that TND may spare one or more nails [8]. Essentially, TND is a mere trachyonychia of the 20 nails.

Epidemiology

Trachyonychia is an insidious disease that most commonly affects children, although no age is exempt [4, 5, 9]. Available data suggests that trachyonychia is either idiopathic, especially in children [5], or a manifestation/association with other cutaneous and non-cutaneous systemic diseases [4, 5]. In children, it is very common for trachyonychia to affect the 20 nails [5], thus the name "TND of childhood."

Baran and *Dupre* [10] observed that several cases of trachyonychia are in fact an expression of alopecia areata (AA). Indeed, later on, *Tosti* et al. [11] reported that the prevalence of trachyonychia among patients with alopecia areata is 3.65%. Other dermatosis that has also been reported with trachyonychia includes eczema, lichen planus, psoriasis, Sezary syndrome, and vitiligo [12–14]. There are also several reports of trachyonychia in association with systemic diseases like sarcoidosis, thyroid disorders, IgA deficiency, amyloidosis, and hemolytic abnormalities (Table 5.1) [4, 12, 14, 15]. However, *Jacobson* and *Tosti* [5] pointed out that several reports regarding trachyonychia and disease associations did not actually correspond clinically to the classic nail changes of trachyonychia.

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Table 5.1 Associations reported with trachyonychia

Associations
Dermatologic diseases
Reported more than once
Alopecia areata [[9–11]
Eczema [9, 16]
Lichen planus [7, 17]
Psoriasis [18, 19]
Pemphigus vulgaris [20, 21]
Vitiligo [22, 23]
Reported once
Darier's disease [24]
Ichthyosis vulgaris [25]
Incontinentia pigmenti [26]
Systemic disorders
Reported more than once
Hematologic abnormalities [9, 27]
Reported once
Allergic rhinitis and bronchial asthma [8]
APECED syndrome [28]
Behcet's disease [9]
IPEX syndrome [29]
Pityriasis rubra pilaris [9]
Reflex sympathetic dystrophy [30]
Selective IgA deficiency [31]
Sarcoidosis [15]
Sezary syndrome [13]
Thyroid disease [9]

Clinical Picture

Trachyonychia was originally described as excess ridging of the nails [6]. Any number of nails can be affected from a single nail to all 20 nails with fingernails being more frequently affected than toenails [32]. The affected nail(s) may show closely spaced longitudinal striations (onychorrhexis) and a dull, rough nail surface, and numerous, small superficial pits may be evident [12, 33]. Two different subtypes of trachyonychia are described by Baran et al. [3, 10], namely, [1] *the opaque trachyonychia* or vertical striated sandpaper 20-nail dystrophy, which is more frequently seen, more severe, and associated with thickened nails, prominent ridging, surface scaling, and sandpaper appearance (Figs. 5.1 and 5.2) [2], and *the shiny trachyonychia* where the nails are uniform, opalescent, and shiny with several reflective shallow pits (Fig. 5.3). Both subtypes may occasionally be seen in the same patient [32]. Koilonychia,

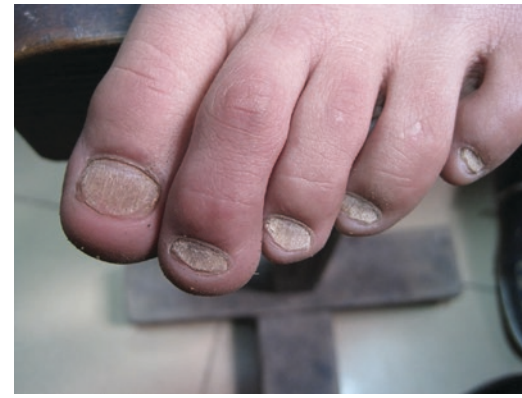

Fig. 5.1 Opaque trachyonychia with sandpaper-like nail plate and koilonychia

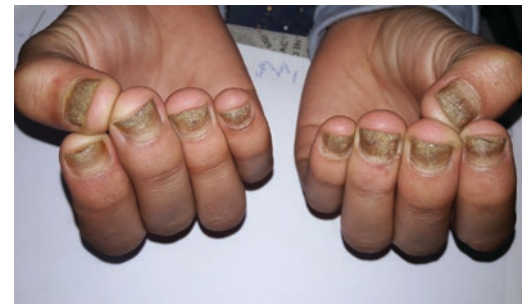

Fig. 5.2 Opaque trachyonychia with nail plate thickening

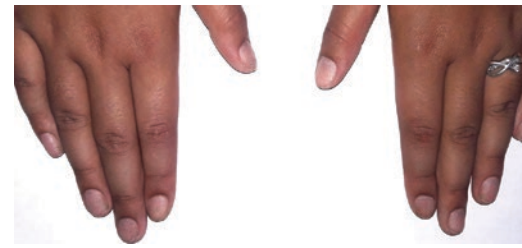

Fig. 5.3 Shiny trachyonychia with numerous shallow pits

nail thinning, fragility, and cuticle hyperkeratosis have also been described with TND/trachyonychia (Figs. 5.4, 5.5, and 5.6) [14, 31]. The nail affection is symptomless [32] although some patients may complain of difficulty in performing fine work especially with the opaque subtype.

When trachyonychia/TND is suspected clinically, it is mandatory for the dermatologist to

Fig. 5.4 Shiny trachyonychia with cuticle hyperkeratosis, spooning, and nail thickening

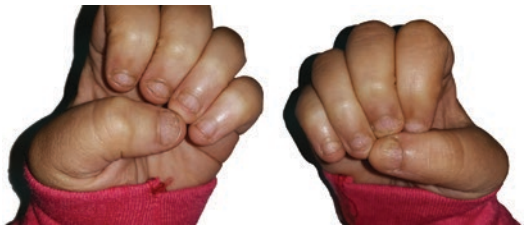

Fig. 5.5 Trachyonychia with nail thinning and distal fragility

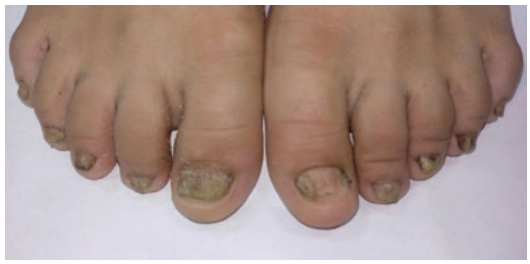

Fig. 5.6 Trachyonychia of toes in teenager football player pronounced over dominant foot

examine for known associations especially AA, psoriasis, and lichen planus (Fig. 5.7). Nevertheless, trachyonychia may precede the classic cutaneous manifestations of these dermatoses. Trachyonychia had been classified clinically into two groups depending on the absence (idiopathic trachyonychia) or presence of associated dermatologic diseases [7].

Etiology and Pathogenesis

As discussed earlier, trachyonychia is believed to be either a manifestation of other dermatologic and systemic diseases or an isolated or idiopathic disorder [12].

Familial cases of trachyonychia/TND had been reported with an autosomal dominant pattern [34]. Balci et al. reported a genetic locus in the form of a balanced translocation XX, t(6q13;10p13) in a mother and daughter with trachyonychia [35]; however, both of their patients also showed anonychia and hypoplasia in several nails. *Gordon* et al. argue that familial cases are likely a representation of the association between trachyonychia and alopecia areata as the latter may occur in a familial manner [12]; moreover, nail changes may follow or precede the onset of alopecia areata by months or years [11].

Trachyonychia is considered a nail aberration which may be caused by several inflammatory diseases that disturb the nail matrix

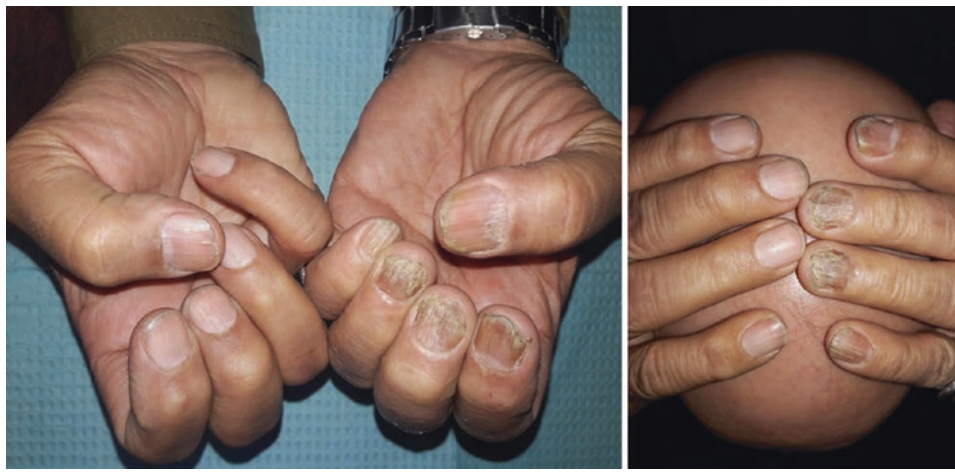

Fig. 5.7 Alopecia totalis and trachyonychia in a middle-aged male

keratinization, but not its mitotic activity [17, 32]. Regardless of the cause, nail matrix onychocytes instead of maturing to form a compact layer of tightly adherent flat cells produce a stratum corneum-like layer that easily desquamates [32]. The course and extent of the matrix inflammatory process and consequently its keratinization are possibly responsible for the different clinical presentations of trachyonychia [7]. A remittent, waxing, and waning inflammatory insult to the nail matrix that never ceases may be responsible for the opaque type of trachyonychia, while an intermittent, focal, and regularly recurrent inflammatory insult to the matrix that is separated by periods of normal matrix function results in the shiny type [36].

Based on the predominant histopathological findings, namely, spongiosis and lymphocytic infiltration, in the majority of patients with idiopathic trachyonychia, it is suggested that this entity may represent a subgroup of endogenous eczema/dermatitis or an autoimmune response confined to the nail matrix [14]. Nonetheless, trachyonychia associated with alopecia areata is suggestive of abnormal keratinization of the proximal matrix with spongiotic changes and lymphocytic infiltration comparable to the idiopathic type of trachyonychia [11, 37].

Pathology

The histopathological changes observed in trachyonychia are usually most severe in the proximal nail matrix in comparison to distal matrix and nail bed [11, 14, 32, 36].

In idiopathic trachyonychia, the majority of patients as reported by Tosti et al. revealed spongiotic changes in the nail apparatus with mild-to-moderate lymphocytic infiltrate in the superficial dermis of the proximal nail fold and nail matrix [7]. The degree of spongiosis ranges from mild to severe changes with intraepidermal microvesicle formation [8]. Dorsal matrix focal hypergranulosis with abnormal eosinophilic appearance of overlying nail plate was also observed.

The nail plates show longitudinal clefts (clinically seen as longitudinal ridging), zones of eosinophilic onychocytes, and zones of parakeratosis (which desquamate and, hence, the ragged appearance observed clinically) [7].

Peculiarly, few patients with idiopathic trachyonychia may show histopathological features of lichen planus or psoriasis without evidence of cutaneous or mucosal affection. Even more bizarre, histopathological features of psoriasis or lichen planus may occasionally be seen in cases of trachyonychia associated with alopecia areata and vitiligo [7, 22, 32, 33].

In trachyonychia with other dermatologic disease, the histopathology of the nail apparatus may coincide with the associated cutaneous dermatosis. Nail matrix lichen planus will reveal an extensive hyperkeratosis, hypergranulosis, lichenoid interface lymphohistiocytic infiltrate, and vacuolar degeneration of basal keratinocytes. Psoriasis would usually involve the proximal nail fold and the nail matrix with hypergranulosis, acanthosis, and focal parakeratosis [14].

As trachyonychia almost never results in permanent nail damage, biopsy from the nail apparatus has been considered unnecessary except in severe, recalcitrant, or uncertain cases [4, 5]. *Haber* et al. suggested implementation of a systemic therapy when histopathological evidence of psoriasis or lichen planus is evident as a primary cause of the trachyonychia [4].

Differential Diagnosis

The unique picture and settings of trachyonychia are usually enough to make the correct clinical diagnosis; however, it is useful to recognize the difference between trachyonychia and the conditions listed in Fig. 5.8 [4, 5, 38–42].

Treatment

A wide range of treatments had been suggested for trachyonychia ranging from topical and systemic medications to ultraviolet therapy and nail

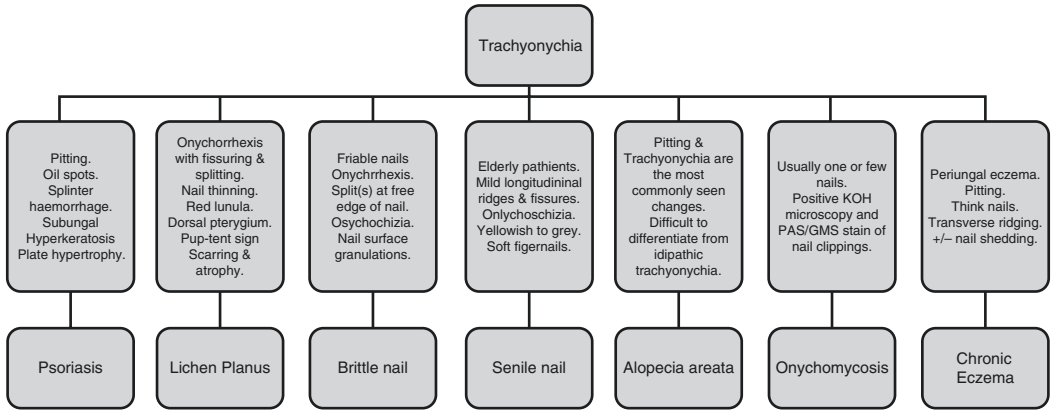

Fig. 5.8 Differential diagnosis of trachyonychia

plate dressings but no standard evidence-based approaches [4, 5, 12]. Unfortunately, most of the available data are from case reports and small cohorts of patients. On the other hand, trachyonychia is mostly a self-limiting disease especially in children who are the most commonly presenting age group of this abnormality, most probably due to an anxious parent(s) [14]. Thus, it is not unwise to consider a nonintervention approach and reassurance for childhood cases with idiopathic trachyonychia.

Topical Therapies

- *Emollients and moisturizers.* One out of three patients with idiopathic trachyonychia showed marked improvement after 2 months of applying a 6% urea cream, while another pediatric patient showed only partial improvement after petrolatum use for 22 months [19, 43].
- *Topical corticosteroids.* Potent topical steroids have been used for the treatment of trachyonychia whether idiopathic or disease associated, but its efficacy is not well documented. Variable responses were reported among six patients with idiopathic and disease-associated trachyonychia [19]. Similarly, the use of topical fluocinonide in eight pediatric patients was not associated with consistent results [43]. Clobetasol propionate under occlusion showed a substantial improvement in one patient [44], and betamethasone dipropionate combination with calcipotriol showed mostly partial response in 39 patients [45].
- *Tazarotene.* Topical un-occluded tazarotene 0.1% gel cleared trachyonychia associated with AA in one patient after 3 months of therapy [46].
- *5-Fluorouracil.* This had been reported successful in one patient with psoriasis-associated trachyonychia [47].
- *Tacrolimus.* One patient with idiopathic trachyonychia showed decreased roughness in all nails after 4 month of 0.1% tacrolimus ointment twice daily [48]. The author had found minor response in several patients with the use of tacrolimus 0.03% ointment under occlusion in combination with weekend clobetasol propionate in idiopathic trachyonychia.
- *Topical PUVA.* This had been reported to be effective in one patient after 7 months of therapy [49].

Intralesional Triamcinolone Acetonide For trachyonychia, intralesional triamcinolone matrix injections are a well-tolerated and effective technique in improving nail texture and functionality [50]. One injection to the proximal nail fold in four pediatric patients showed a 42% decrease in

pitting after 4 months [51]. Eleven of 19 patients (58%) treated for 6 months with intralesional triamcinolone at 4-week intervals showed improvement between 75% and 100% in their trachyonychia [52].

Systemic Therapies

- *Acitretin.* After 7 months of 0.3 mg/kg/day, acitretin was effective in clearing the nails of one patient with occupational trachyonychia due to psoriasis [53]. Excellent results were reported in a female patient with hypothyroidism and trachyonychia after 7 months of acitretin and clobetasol 8% nail lacquer for 10 months [54].
- *Alitretinoin.* More than 75% improvement was observed in 66.7% of a small cohort of patients after 6 months of alitretinoin 30 mg/day for idiopathic recalcitrant trachyonychia. Adverse event occurred in 42.9% of patients, and two (9.5%) withdrew from the study due to headache [55].
- *Biotin.* Oral administration of biotin 2.5 mg/day for 180 days reduced longitudinal ridging, thinning, and distal notching in two girls with idiopathic trachyonychia [56].
- *Cyclosporine.* The mean depth of nail roughness in four out of five patients with psoriatic trachyonychia improved after 3 months of cyclosporine treatment at a dose of 3 mg/kg/day [57]. *Oh* and *colleagues* recently showed a significant clinical response in 38 patients treated with cyclosporine 3–5 mg/kg/day with a pantothenic acid-complex-based dietary supplement in comparison to those treated with the dietary supplement alone. The latter authors reported that cyclosporine therapy group had more patients whose improvement was almost clear or whose improvement was marked or moderate than the control group. Moreover, the Dermatology Life Quality Index (DLQI) was significantly lowered in the cyclosporine group in comparison to the controls. Mild adverse effects in 10.5% of patients in the cyclosporine group were reported [58].
- *Corticosteroids.* Oral mini-pulse betamethasone (4 mg once daily for two consecutive days/week) cleared idiopathic trachyonychia after 6 months of therapy in a 12-year-old girl [59].

There is no gold standard therapy for trachyonychia, and the fact that many cases resolve spontaneously may deem treatment unwarranted. However, combination therapy may be helpful in recalcitrant trachyonychia, and it may also help minimize adverse events of systemic treatments by reducing drug dosage (Fig. 5.9). As trachyonychia is a self-limited disease, it is sensible to start with topical medications for 2–3 months and then add intralesional triamcinolone if no improvement is noticed, and finally, a systemic agent may be added in resistant cases.

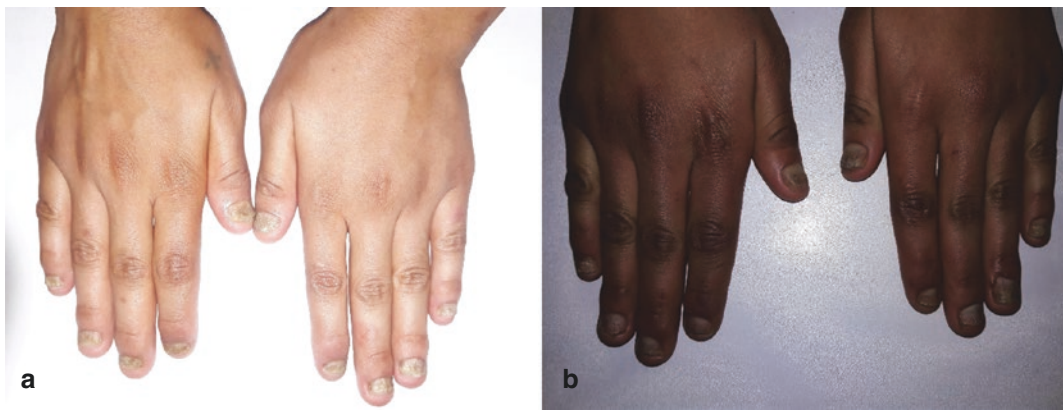

Fig. 5.9 Idiopathic trachyonychia before therapy (**a**) and 2 months after cyclosporine 50 mg/day and intralesional triamcinolone once monthly (**b**)

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6 In Vivo and Ex Vivo Confocal Microscopy for Nail Diseases

Diletta Fiorani, Jean Luc Perrot, Pietro Rubegni, and Elisa Cinotti

Reflectance confocal microscopy (RCM) is a noninvasive high-resolution imaging technique that has been applied in dermatology for the diagnosis of melanocytic and non-melanocytic tumors and inflammatory and infectious diseases and, in the last years, also for the examination of skin appendages such as hairs and nails. It allows a noninvasive and in vivo examination of the nail plate, potentially reducing the number of biopsies that can irreversibly alter the structure of this sensitive area. RCM represents a valid tool for the diagnosis of onychomycosis and has shown better sensitivity and specificity than the microscopic examination with KOH preparation. Regarding melanonychia, it is unable to explore nail matrix owing to the limited penetration depth, but it can be used intraoperatively to visualize melanocytes in the nail matrix since the eponychium can be reclined during the surgical biopsy. Ex vivo fluorescence confocal microscopy (FCM) can also play a role in the preoperatory diagnosis of other nail tumors such as squamous cell carcinoma, onycholemmal carcinoma, onychomatricoma, onychopapilloma, glomus tumors, or neurinoma; it allows to perform a quick examination before final histopathology and to outline tumor margins. In the future, RCM could be used for a noninvasive diagnosis of inflammatory nail disease and to monitor the response to topical or systemic therapy. Limitations are the higher cost, the requirement to have experienced specialized dermatologists for the acquisition and interpretation of the images, and the limited achievable depth.

In memory of Bruno Fouilloux.

Confocal Microscopy and Nails

Confocal microscopy has been developed by Marvin Minsky in 1955 [1]. Since 1993, it has been applied in vivo in the field of dermatology [2]. It provides real-time high-resolution black and white horizontal sections of the entire epidermis and superficial dermal layer up to ~200 μm of depth. Unlike conventional microscopes, confocal microscopy enables to create virtual sections inside the skin and to identify also dynamic events such as blood flow [3]. Confocal microscopy can be used in the reflectance or the fluorescence mode. In reflectance confocal microscopy (RCM, 830 nm laser), different contrast depends on the refractive index of the inner structures: melanin and keratin are endogenous chromophores; therefore, stratum corneum, hair shaft, acrosyringium, pigmented

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keratinocytes, and melanocytes appear hyperrefractive [4]. Images appear in grayscale with dark hyporeflective structures (black and dark gray) and bright hyperreflective structures (white and light gray). In fluorescence confocal microscopy (FCM, laser wavelength of 488 nm and 658 nm), the nonfluorescent structures are dark (black and dark gray), and the fluorescent structures are white. Autogenous fluorescence of the skin and/or fluorescent agents can be exploited. In vivo confocal microscopy is mainly used in the reflectance mode, and fluorescence mode is practiced for research, whereas in ex vivo conditions, both reflectance and fluorescence modes are used, and reflectance and fluorescence can be also used simultaneously (fusion mode). In ex vivo conditions, several fluorescent agents have been tested, including acridine orange, fluorescein, patent blue, methylene blue, Nile blue, and toluidine blue, but only acridine orange is used in practice, as it provides strong contrast for cells by staining nuclear DNA. With acridine orange, the nuclei of the cells are fluorescently stained in white with an increase in contrast of keratinocytes, hair follicle epithelium, sebaceous and eccrine glands, fibroblasts, and tumor cells relative to the surrounding tissue.

Three devices dedicated to the skin are commercially available: two work in vivo (VivaScope 1500 and 3000, Caliber, New York, USA, distributed in Europe by the company MAVIG GmbH, Munich, Germany) and one ex vivo (VivaScope 2500, Caliber). The traditional wide probe camera VivaScope 1500 can work in both reflectance and fluorescence modes, provides images of 500 μm in diameter that can be stitched together in mosaic images of maximum 8 mm and should be fixed to the tissue with a special window, and needs mineral oil as interface. The convex surface of the nail and the concavity of the transition between the nail plate and the surrounding skin make difficult to place and hold the device during in vivo imaging. To overcome this technical problem, the handheld device (VivaScope 3000) can be used for the nail. VivaScope 3000 with ultrasound gel used as interface is better than VivaScope 1500 for nail examination because no extra window is needed, and the ultrasound gel allows adapting the tip of the device to the irregular nail surface to be observed. The second generation of VivaScope 3000 is more suitable than the newest version of VivaScope 3000 due to its smaller tip of 0.5 cm instead of 1.5 cm. The handheld camera acquires single images of 920 μm in diameter in reflectance mode, and no mosaics are obtainable. The acquisition of in vivo images is fast; it takes just a few minutes, especially with the handheld camera. Optical resolution is in the cellular scale: <2 μm in the horizontal plane and <5 μm in the vertical plane. The ex vivo device is used on freshly excised unfixed and not cut surgical specimen. Notably, it does not modify the tissue and does not prevent subsequent histopathological examination. Different from in vivo examination, ex vivo examination gives the opportunity to observe the sample from its lateral sides and its bottom according to how the specimen is mounted. The ex vivo microscope produces horizontal images of 750 × 750 μm of the different layers of the skin up to a thickness of 200 μm [5]. Single images are automatically stitched together into a reconstructed mosaic image to a maximum size of 20 × 20 mm [5]. The lateral and axial spatial resolutions are 1 μm and 3 μm, respectively.

RCM has been used in clinical routine for the diagnosis of several melanocytic and nonmelanocytic tumors [6–8], and it has been demonstrated to be superior to dermoscopy for the diagnosis of melanoma [9]. More recently, it has also been applied for different diseases such as psoriasis, atopic dermatitis, lichen planus, mycosis fungoides, discoid lupus erythematosus [10–15], and cutaneous infections and infestations [16, 17] and for the examination of skin appendages, such as hair [18] and nails [19, 20].

Healthy Nail

Nails are particularly suitable to be examined with RCM owing to the nail plate transparency that allows a deeper penetration of the laser up to 400–500 μm [20]. In 1995, Kaufman et al. affirmed that the examination of nail apparatus with conventional light microscope, transillu-

mination, and reflected light illumination was not useful because of the high reflectivity of the keratinized surface of the nail plate, and they first considered RCM as a new instrument for the study of nail unit in vivo [19]. Their microscope allowed to visualize not only changes seen in the capillary nail fold but also the nail plate and nail bed. Lower nail plate showed discrete cells, some with nuclear fragments, which were visible as bright spots; underlying epithelial ridge in nail bed revealed keratogenous zone and underlying rootlike epidermal ridges [19].

In 2011, Sattler et al. have described the morphology of nail unit under in vivo RCM [21]. Nail surface, nail plate, and nail bed in thin nails (<500 μm) could be examined with handheld RCM (Fig. 6.1). The difference of intensity of reflection allowed to distinguish three different layers:

- A superficial layer with a brighter reflection
- An intermediate layer with slightly poorer signal
- A deeper brighter zone

Furthermore, transition zones have been described [20, 21]:

- A transition area to the underlying nail bed that shows wavelike structures, which are directed toward the fingertip
- A transition area between the proximal nail plate and the skin that is characterized by three adjacent layers:
  - (i) Normal honeycombed pattern of the epidermis
  - (ii) Stellate-shaped epidermal keratinocytes, i.e., keratinocytes sectioned obliquely
  - (iii) Hyperreflective or moderate reflective band representing cuticle

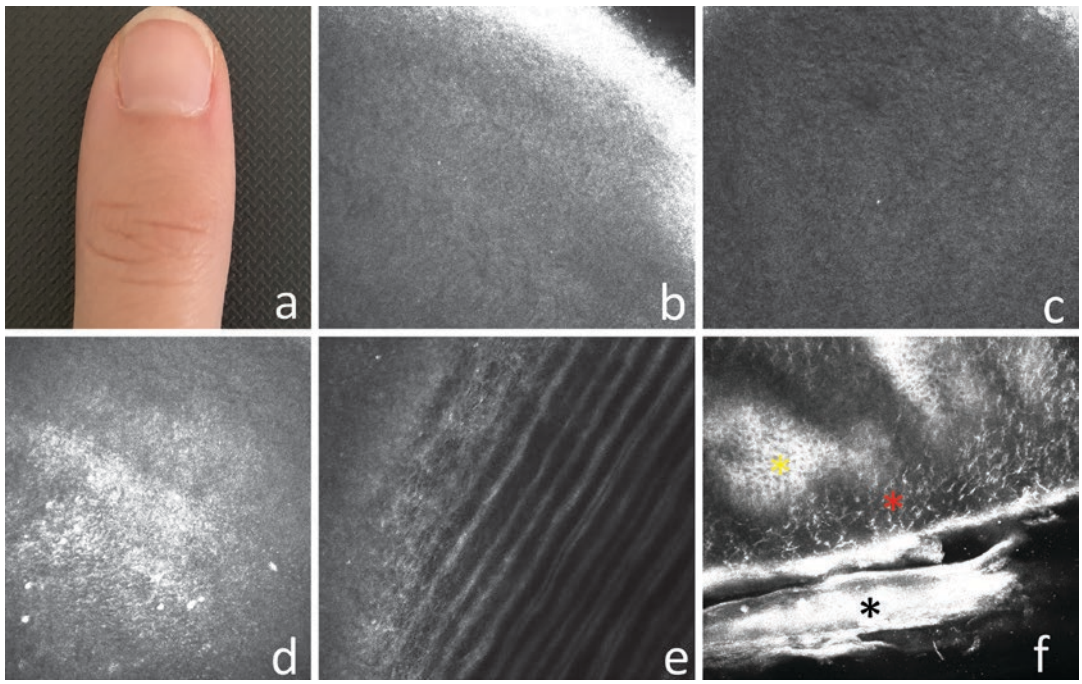

Fig. 6.1 Clinical (**a**) and in vivo reflectance confocal microscopy (RCM) aspect of a thumbnail plate (**b**–**f**). Three zones of different brightness can be differentiated going deeper into the nail plate: a bright surface (**b**), a dark central part (**c**), and a bright deepest part (**d**). The transition to the underlying nail bed is visible as wavelike structures, which are directed toward the fingertip (**e**). The transition between the proximal part of the nail plate and the skin (**f**) is characterized by normal honeycomb pattern of the epidermis (yellow asterisk) that continues into stellate figures corresponding to epidermal keratinocytes sectioned obliquely (red asterisk) and by a hyperreflective stripe corresponding to the cuticle (black asterisk)

Onychomycosis

Onychomycosis is a very common fungal infection of the nail caused by dermatophytes, yeasts, or molds [22]. It represents about 50% of ungual pathology [23]. Its diagnosis can be challenging because it is often difficult to distinguish from other nail disorders such as traumatic onycholysis, psoriasis, or lichen ruber planus [24]. Treatment often requires several months of systemic medication and can cause serious adverse reactions such as hepatitis or drug-induced lupus erythematosus [25]. Therefore, mycologic study is required before antifungal therapy is prescribed. Conventional diagnostic methods include KOH preparation for optical microscopy examination, culture, PCR, and histopathology with PAS staining [26].

KOH preparation is a cheap and easy to execute method that provides a result after about 30 minutes. However, it is invasive, and the sample collection must be correct in order to avoid false-negative results or false-positive results such as contaminant molds [27]. Dermatophyte culture allows the identification of the fungal species, but it takes a long time and can be contaminated. Recently, distinctive dermoscopic signs of distal subungual onychomycosis have been described such as jagged proximal edge with spikes of the onycholytic area and longitudinal striae [28, 29]. Utility of in vivo RCM for the diagnosis of onychomycosis has been known since 1994 when Pierard et al. considered RCM as "a door opened to the future," able to help clinician in the identification of onychomycosis [30]. The first case of onychomycosis confirmed by in vivo RCM was reported by Hongcharu et al. in 2000 [31]. RCM revealed network of branched high-reflective hyphae just below the surface of the nail plate (Fig. 6.2) and was able to confirm the diagnosis with higher precision and faster results compared with KOH preparation. However, other authors asserted that this tool is too expensive to be used in clinical practice [27].

In 2012, Rothmund et al. considered 50 patients with suspected onychomycosis and compared sensitivity and specificity of six diagnostic methods including in vivo RCM [32]. RCM analysis was performed with VivaScope 1500 on the most suspicious area. Diagnosis of onychomycosis was made when hyper-refractive lengthy structures and bright aggregates (corresponding to spores) were observed. RCM had

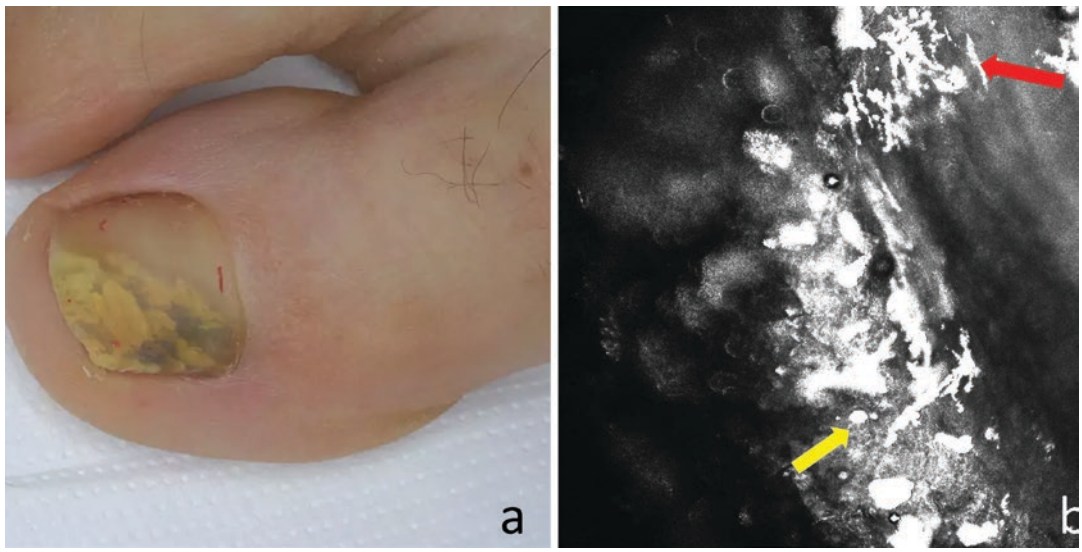

Fig. 6.2 Clinical (**a**) and in vivo reflectance confocal microscopy (RCM, **b**) aspect of onychomycosis. RCM shows characteristic highly reflective thick linear structures (red arrow) corresponding to hyphae and roundish hyperreflective structures (yellow arrow) corresponding to spores

better sensitivity (79% vs. 74%) and specificity (81% vs. 76%) than KOH preparation. Fungal culture showed the lowest sensitivity and the worst negative predictive value. PCR showed the highest sensitivity, followed by RCM, PAS, and KOH preparation. RCM and KOH showed a high specificity, and RCM exhibited the best positive predictive value. RCM can also provide information about location and density of fungal cells [33]. Nevertheless, only PCR and culture allow identification of species. It is not clear if RCM is able to distinguish dermatophytes from molds or yeasts since no specific RCM studies have been conducted yet [33, 34].

Melanonychia

A big variety of conditions present longitudinal pigmented bands on the nail plate including melanocytic nevus, malignant melanoma, lentigo, ethnic melanonychia, pigmented onychomycosis, pigmented Bowen's disease, drug-induced hyperpigmentation, and subungual hematoma [35]. The prevalence of melanonychia is approximately 1% [36]. Dermoscopy is a useful tool which can better identify the cases in which pathological examination is indicated [37]. With RCM, it is possible to visualize melanocytes of Hutchinson's sign (Fig. 6.3), but melanocytes of the nail bed are dif-

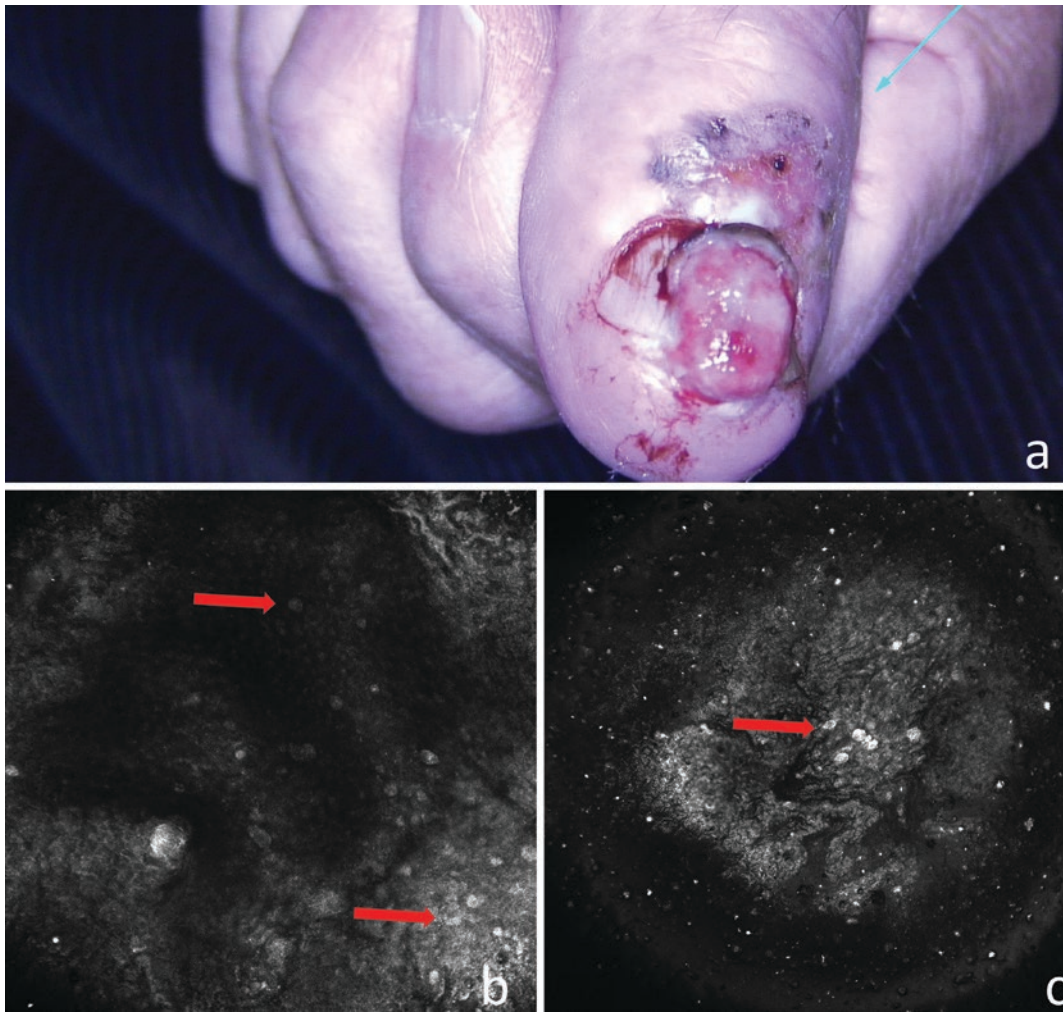

Fig. 6.3 Clinical (**a**) and in vivo reflectance confocal microscopy (RCM) aspect of Hutchinson's sign (**b**) and of the nodular part (**c**) of a subungueal melanoma. In vivo RCM shows hyperreflective roundish big cells corresponding to tumoral melanocytes (red arrow)

ficult to be identified (Fig. 6.4), and nail matrix is impossible to be observed owing to the limited penetration depth. Debarbieux et al. tried to evaluate the feasibility of an intraoperative diagnosis by in vivo RCM [38, 39] since the eponychium could be reclined during the surgical biopsy to visualize nail matrix pigmentation. Four different patterns were identified: pattern 1: numerous atypical bright roundish cells at the dermoepithelial junction, usually associated with dendritic cells (pagetoid cells were occasionally identified in a few cases); pattern 2: numerous nests; pattern 3: very bright cobblestone pattern; and pattern 4: variably densely distributed dendritic basal cells, with neither nests, roundish cells, nor atypical cells in the dermis. Pattern 1 was the most relevant for melanoma diagnosis, pattern 2 usually indicated the presence of acral nevus, pattern 3 could be associated to melanoma, and pattern 4 could be found either in very early in situ melanomas or in lentigo with slight melanocytic hyperplasia [40]. Correlation with histopathology was good, and perioperative in vivo RCM allowed an extemporaneous diagnosis and one-step surgical treatment, thus reducing the pain induced by multiple invasive surgical procedures on the nail apparatus, as well as the postoperative disability period. Moreover, if in vivo RCM is unable to provide a sure diagnosis, ex vivo confocal microscopy can be used. Ex vivo confocal microscopy could be particularly useful for nail tumors in order to confirm intraoperatively the diagnosis of the biopsy specimen and to proceed to the final excision without waiting for the histological examination. Notably, it is more suitable than the optical examination of frozen sections of this site because nail tumors are often very small in size, and it is desirable that no material is wasted in producing sections that subsequently cannot be submitted to conventional histopathology [5]. Debarbieux et al. also used the in vivo device for the ex vivo examination of nail biopsies of pigmented subungual melanoma in a series of eight cases [38]. However, this procedure has limitations in that the specimen is not fixed, tends to move, and is difficult to orient, unlike when using the dedicated ex vivo device.

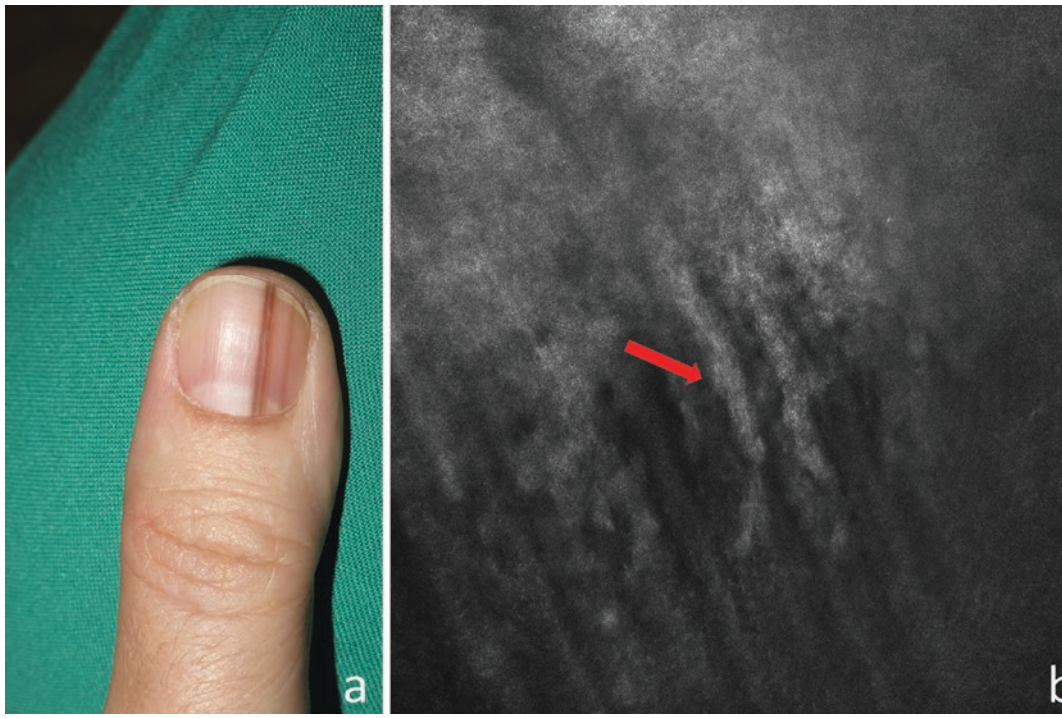

Fig. 6.4 Clinical (**a**) and in vivo reflectance confocal microscopy (RCM, **b**) aspect of a junctional nevus. Small and regular melanocytic nests are visible along the nail bed (**b**, red arrow)

Other ungual tumors different from melanoma can present with melanonychia striata. Fernandes Massa et al. have described a case of pigmented squamous cell carcinoma (SCC) of the nail bed [41]. In vivo and ex vivo confocal microscopy of the distal matrix were performed intraoperatively: in vivo RCM showed small, bright nonnucleated cells corresponding to pigmented keratinocytes; a cobblestone pattern; and rare, small dendritic cells. The proximal nail bed revealed large, roundish structures with small, bright cells at their periphery within the papillary dermis, which were different from atypical melanocytes. These roundish structures could be better visualized with ex vivo RCM which showed small, bright nonnucleated cells with a structureless center [41].

RCM represents also a preliminary screening instrument for nail matrix nevus. Only two case reports have been described: both cases showed hyperreflective roundish cells in the deeper part of the nail plate that were uniform in size and shape and seemed to correspond to melanocytes on histopathology [42]. However, it should be noticed that these cells are difficult to differentiate from hyperreflective corneocytes that can be found in case of onycholysis and that no comparison with malignant melanocytes has been reported yet. Interestingly, in both nevi, no dendritic hyperreflective cells were observed. In our experience, we found that in nevi, when the nail bed was reachable, we could observe an alteration of the transition area from the nail plate to the underlying nail bed: wavelike structures were thickened and greyish and formed cord-like structures with some bulbous projections that remind cutaneous melanocytic nests under RCM (Fig. 6.4). It should be observed that in vivo RCM can be also used to examine skin lesion destroying the nail plate such as in case of malignant tumors (Fig. 6.3).

Nonpigmented Nail Tumors

Although most of the nonpigmented nail tumors are of epithelial origin, amelanotic melanoma can occur. The diagnosis of these tumors is often challenging and delayed because they can mimic other nail disorders such as onychomycoses, onychodystrophy, and verruca vulgaris [43–45].

SCC is the most common malignant tumor of the nail apparatus and usually presents in the form of Bowen's disease and amelanotic melanoma [46]. Fingernails are selectively affected, especially the thumb [45]. Its RCM and FCM features are well described both in vivo and ex vivo in the skin but are less studied in the nail. Amelanotic subungual melanoma represents only a small fraction of all malignant melanomas [43], and it usually manifests as a vascular or ulcerating nodule [47]. RCM recognizes amelanotic melanocytes, but this aspect has not been deeply studied for the melanoma of the nail apparatus [20].

A pilot study conducted on ten patients with nonpigmented nail tumors (four in situ SCC, two invasive epithelial tumors, three benign epithelial tumors, and one nodular melanoma) has described for the first time the microscopic features examined with the ex vivo FCM [48]. Images were taken intraoperatively on the surgical specimens after immersion in acridine orange, a specific staining of the nucleus. Invasive SCC of the nail matrix and onycholemmal carcinoma showed well-demarcated epithelial nests composed of cells with nuclear pleomorphism (variable size and shape of the nucleus) invading the dermal area. Therefore, in these cases, it would be possible to perform wide excision of the tumors just after the observation of a biopsy specimen under ex vivo FCM shortening the management. In situ SCC displayed cytoarchitectural atypia: roundish cells in the upper layers of epithelium corresponding to dyskeratotic keratinocytes and "blurred cells," i.e., large pseudoacanthotic cells with blurry limits [48]. However, it was impossible to distinguish epithelial cells from inflammatory cells or atypical melanocytes using the fluorescence mode after acridine staining because acridine stains nuclei of cells of different nature.

Benign tumors were also observed with ex vivo FCM [48]. In particular, onychomatricoma exhibited epithelial proliferation with acanthosis and papillomatosis without atypia;

moreover, small fusiform cells corresponding to fibroblasts were observed inside the papillae (Fig. 6.5) [48]. Onychomatricoma has also been examined with in vivo RCM (Fig. 6.6) [49, 50]. Sanchez et al. have described multiple parallel channel-like structures through the nail plate that correspond to the digitating fibroepithelial projections arising from the matrix [49].

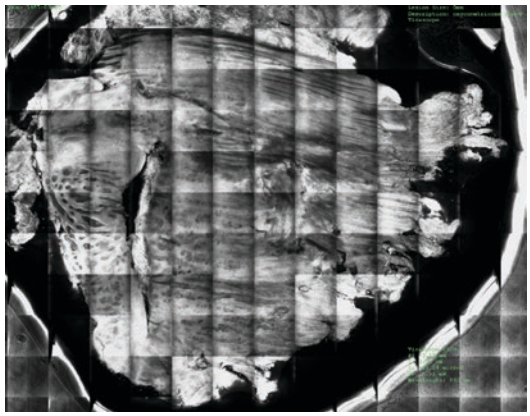

Fig. 6.5 Ex vivo reflectance confocal microscopy shows the general architecture of an onychomatricoma

These cavities appeared hyporeflective and were surrounded by a brighter matrix epithelium (Fig. 6.6a). Their hyporeflectance could be induced by their content in serum and blood which have low refraction of light on RCM [50]. If in vivo RCM is used perpendicularly to the distal ungual margin, hyporeflective roundish areas corresponding to the transversal sections of the tumor cavities can be observed (Fig. 6.6b) [50]. Onychopapilloma is a very circumscribed epithelial tumor of the nail bed, characterized by thin digitiform epithelial projections within the upper dermis that were visible under ex vivo FCM [48]. Not only nonpigmented epithelial tumors can be recognized under ex vivo FCM but also other amelanotic non-epithelial tumors such as glomus tumor and neurinoma [5].

Leukonychia

Leukonychia is a white discoloration of the nail; apparent and true variants have been described. Apparent leukonychia derives from pathological

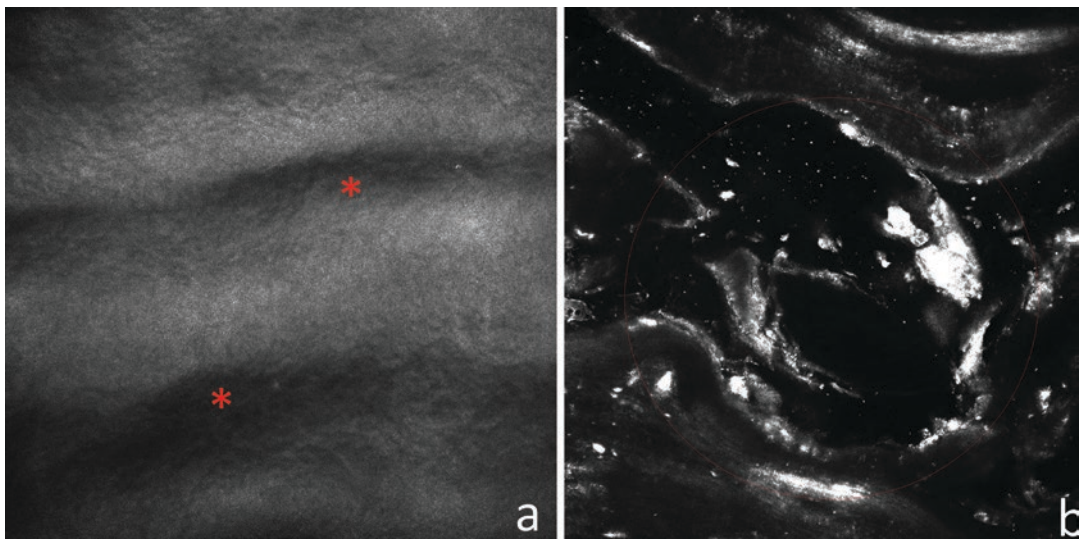

Fig. 6.6 In vivo reflectance confocal microscopy (RCM, **a**,**b**) aspect of onychomatricoma shows the top of the nail channel-like structures inside the nail bed (**a**, red asterisk) and the vertical section of the nail channel-like structures at the free edge of the nail (**b**, red circle)

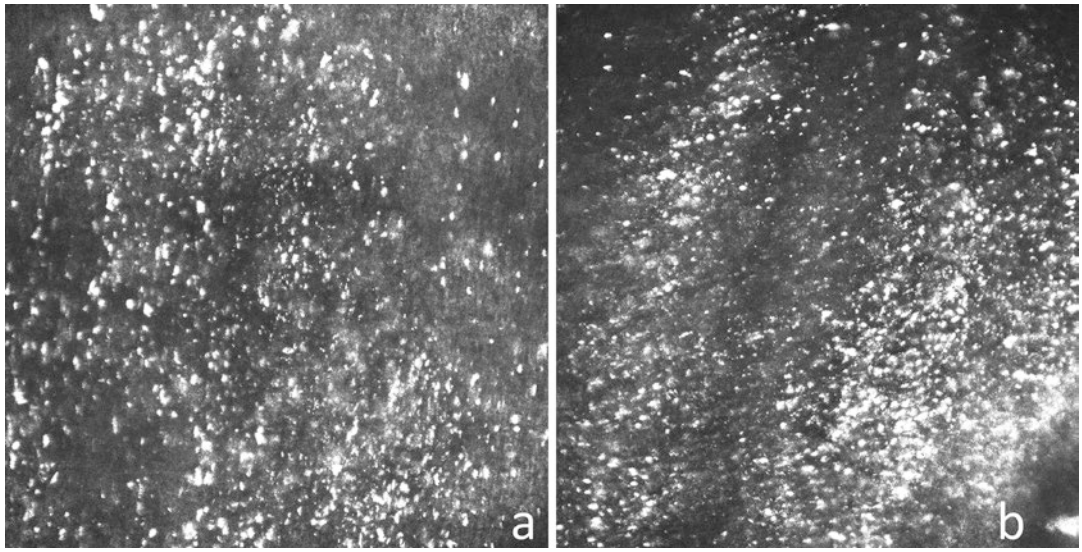

Fig. 6.7 In vivo reflectance confocal microscopy (RCM) aspect of the nail plate in case of leukonychia (**a**) and a subungual hematoma (**b**) detachment of single hyperreflective corneocytes that is visible

changes (e.g., edema) in the nail bed, whereas true leukonychia results from disorder of keratinization occurring in the nail matrix with a consequent involvement of the nail plate itself [51]. When an external process alters the nail plate's growth, the discoloration of the nail plate is called pseudoleukonychia.

Main in vivo RCM features of leukonychia were first described by Sattler et al. in 2012 [21]; in vivo RCM revealed detachment of single hyperreflective corneocytes (Fig. 6.7). However, it is well known that white discoloration of the nail can be a sign of different diseases such as trauma and lichen planus, and there is no study in literature which has described the differences in the morphology or amount or depth of dyskeratotic corneocytes [20].

Inflammatory Disorders

Unlike inflammatory skin diseases, inflammatory nail pathologies have not been studied in detail with in vivo RCM microscopy. Only few cases of nail psoriasis have been described [20], and they showed large hyperreflective irregular areas on the surface and inside of the nail plate corresponding to hyperkeratosis (Fig. 6.8). The lateral margins of the nail displayed delamination of the nail plate [20].

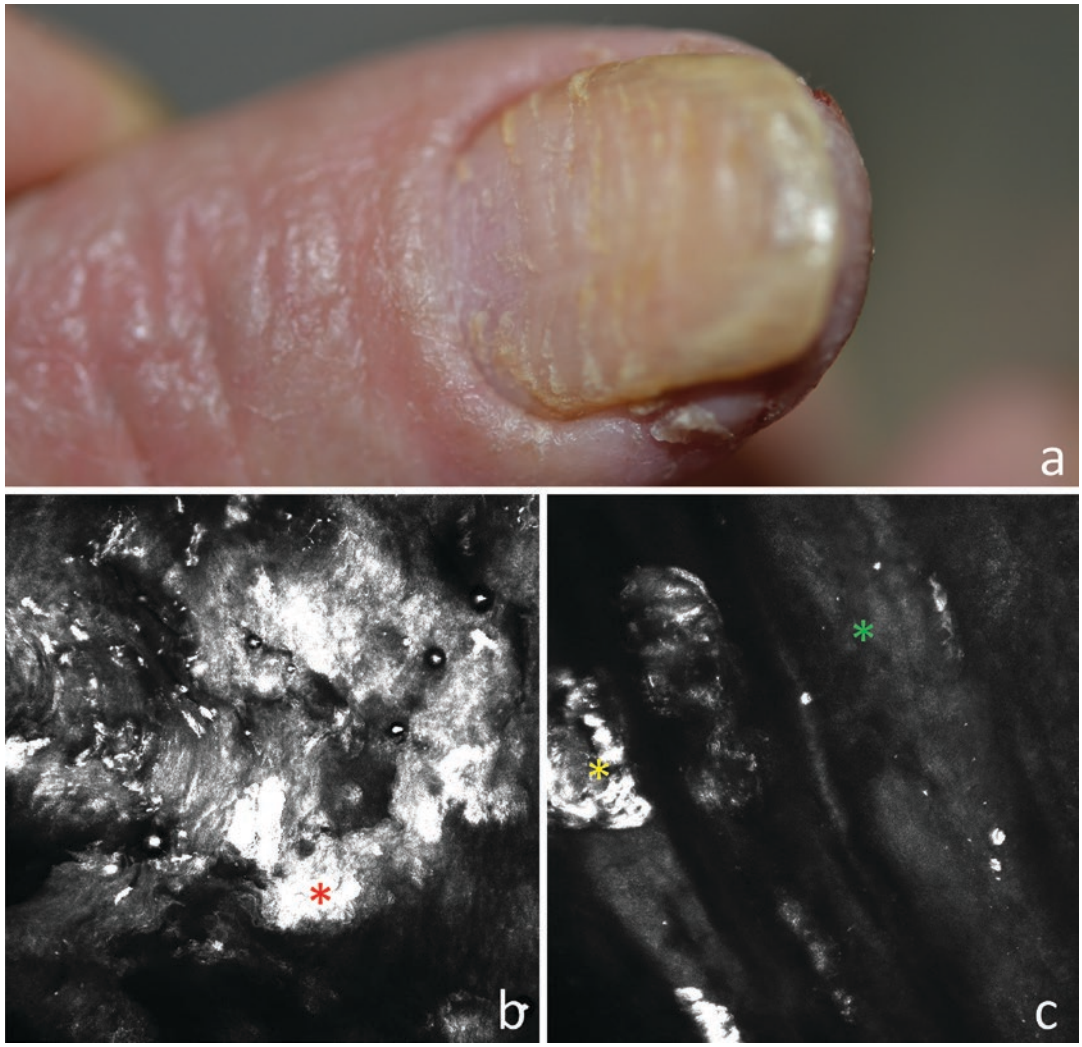

Fig. 6.8 Clinical (**a**) and in vivo reflectance confocal microscopy (RCM, **b**,**c**) aspect of nail psoriasis. In vivo RCM shows large hyperreflective irregular areas on the surface of the nail plate (red asterisk) (**b**) and inside the nail plate (yellow asterisk) (**c**), likely corresponding to areas of keratin densification. Normal nail plate is also visible (green asterisk)

Conclusion

RCM and FCM are noninvasive diagnostic techniques that can be used for a better evaluation of nail diseases. In vivo RCM represents a promising adjunctive diagnostic tool for the diagnosis of onychomycoses and for other nail plate diseases. The in vivo examination does not require any sample collection; the probe can be applied directly to the nail surface without any preparation, and it permits to quickly evaluate the entire nail plate. In some cases, in vivo RCM allows to avoid biopsies that cause pain and discomfort to the patient and can irreversibly alter the nail growth. In the future, RCM could also be used for noninvasive diagnosis of inflammatory nail disease and to monitor the response to topical or systemic therapy. In vivo RCM is often not able to explore the nail bed and cannot explore the nail matrix because the nail thickness restricts laser

penetration. However, it can represent a very useful tool for the examination of the nail bed and the nail matrix if used intraoperatively after reclination of the nail plate and/or eponychium. Limitations are the higher cost than traditional optical microscope or dermoscopy, the need to have experienced specialized dermatologists for the acquisition and interpretation of the images, and the limited achievable depth.

In cases in which biopsies are necessary, ex vivo RCM and FCM can be performed intraoperatively immediately on the surgical tissue to have a quick examination before final histopathology. Ex vivo RCM is more suitable for melanocytic skin cancers, whereas ex vivo FCM is more suitable for non-melanocytic skin cancers.

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7 Innovative Therapies in Nail Disorders

Smail Hadj-Rabia

Introduction

Recent advances in biology and bioinformatics have led to a much deeper understanding of the genetic underpinnings of disease and drug targets. In the field of genodermatoses, the detection of mutant alleles, in new genes and/or previously known genes, is now allowed in low as 1% of cells in a skin sample through parallel sequencing (or next-generation sequencing). Therefore, the extensive acquisition of significant data permits (1) a better classification of these rare disorders, (2) the identification of signaling pathways to which belong the proteins encoded by those genes, and (3) finally the identification of promising therapeutic targets. During the last decade, this was particularly true for mosaic disorders and ectodermal dysplasias (EDs).

Mosaic Disorders

Mosaicism has traditionally been defined as the coexistence of at least two genotypes in an individual derived from a single zygote, and this was considered to be an abnormal state. Neonates may present with "normal range" birthmarks that are the manifestation of cutaneous mosaicism [1]. Acquired mutations in the *FGFR3* gene may explain late seborrheic keratoses. Finally, we are all mosaic by this definition, owing to a strikingly high but normal postzygotic mutation rate in utero. Therefore, Kinsler et al. propose to define a mosaic abnormality of the skin as the coexistence of cells with at least two genotypes, by the time of birth, in an individual derived from a single zygote, and which leads to a disease phenotype. For example, distinct clinical entities such as congenital lipomatous overgrowth vascular malformations, epidermal nevi, scoliosis/skeletal and spinal (CLOVES) syndrome, fibroadipose overgrowth (FAO), megalencephaly-capillary malformation (MCAP), and some cases of isolated macrodactyly or Klippel-Trenaunay syndrome (KTS) are now related to postzygotic activating mutations of *PIK3CA* gene. To avoid any further confusion in the field, the umbrella term of *PIK3CA*-related overgrowth spectrum (PROS) designates known and emerging phenotypes caused by postzygotic *PIK3CA* mutations [2]. The main feature of PROS is congenital, sporadic, and segmental overgrowth of adipose, muscle, skeletal, and/or cerebral tissue. Patients presenting with PROS were treated with supportive care including surgery, sclerotherapy, and psychology.

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PIK3CA gene encodes the p110a catalytic subunit of the phosphatidylinositol 3-kinase and is involved in cell proliferation, motility, survival, and metabolism. PIK3CA belongs to the PIK3-AKT-mTORC pathway. Allosteric mTORC inhibitors, such as sirolimus, are used for posttransplant immunosuppression. An open-label study in 39 PROS patients receiving a low dose of sirolimus suggests a modest reduction of overgrowth. In parallel, several PIKC3A inhibitors are under development as treatments for oncological conditions, where gain-of-function mutations in *PIK3CA* are identified [3]. Among them, BYL719 shows the dose- and time-dependent inhibition of the PI3K/AKT pathway in *PIK3CA*-dependent xenograft tumor. BYL719 has good tolerability in clinical trials in patients with *PIK3CA*-dependent tumors. BYL719 was therefore administrated orally once a day to 19 patients with PROS who had life-threatening complications. All the patients carry a PIK3CA mutation. In addition to the clinical improvement (reduction in the size of the hypertrophy), a radiological response in all patients was noted. After 90 and 180 days of therapy, the mean volume of the target lesions had decreased by 27.2 ± 14.6 and 37.8 ± 16.3%, respectively. Repositioning an innovative molecule (BYL719) under investigation in oncology for patients with a genetic disorder remains fascinating [4].

Ectodermal Dysplasias

Ectodermal dysplasias comprise a large clinically and etiologically heterogeneous group of genetic disorders that are characterized by abnormalities in tissues derived from the embryonic ectoderm. Initial classification systems for the EDs predate molecular genetics and were categorized and grouped according to phenotypic features and mode of inheritance. The most widely known such nosology was developed by Dr. Newton Freire-Maia in the 1970s and included conditions with "classical signs" involving hair, teeth, nails, and/or sweat glands [5]. The disorders were subdivided into Group A, those having at least two of these tissues affected, and Group B, conditions affecting one of the aforementioned tissues and at least one other tissue of ectodermal origin (e.g., mammary gland) [5]. This classification remained difficult to use for daily practice.

In 2017, an international working group of individuals met on the National Institutes of Health campus in Bethesda, Maryland. The definition of ED was refined, and a classification was proposed. This classification incorporates phenotype, inheritance, and molecular etiology including developmental pathways or structural assembly to organize and cluster the ED conditions [6].

To include the broad variety of tissues that derivate from the ectoderm and to mention dysfunction of ectodermal derivatives that may a normal "morphological" aspect, the following consensual definition of ED was proposed: EDs are genetic conditions affecting the development and/or *homeostasis* of two or more ectodermal derivatives, including hair, teeth, nails, and *certain* glands. Sweat glands was replaced by certain glands, and homeostasis was added. Genetic alterations of ED-associated genes that only affect one derivative of ectoderm (e.g., hair, teeth, nails, sweat glands) should be grouped as nonsyndromic traits of the causative gene (e.g., nonsyndromic hypodontia or missing teeth associated with pathogenic *EDA* variants).

To further develop a useful classification including recent genetic knowledge and involved pathways, the following points were discussed:

- Conditions already included as part of other classifications or groups of diseases and/or presented in different chapters in textbooks (e.g., vesiculobullous disorders) were not included, although they may be associated with alterations in ectodermal structures.
- Complex syndromes that have ED signs but also major non-ED signs (e.g., affecting the bone, brain) were also excluded (e.g., trisomy 21).
- Conditions listed in OMIM with only one case report and no known molecular etiology were excluded.

Therefore, from the 186 ED reported in 2013, 97 were finally retained. They were grouped based on genotype, molecular pathway, and phenotype. Three major molecular pathways gather most of the ED phenotypes and involved genes: the EDA, WNT, and TP63 pathways, respectively. Further clinical investigations will probably identify specific features for each pathway. For example, nails seem to be normal in the syndromes belonging to the EDA pathway, while hyponychia are more frequent for those associated with the WNT pathway.

The most frequent ED phenotype is known as ectodermal dysplasia 1, or hypohidrotic X-linked ED or Christ-Siemens-Touraine syndrome (MIM305100). It is characterized by hypohidrosis or anhidrosis, spoon-shaped nails, hair anomalies (hypotrichosis, absent or scanty eyelashes and eyebrows, and fine scalp hair), and teeth anomalies (hypodontia with conical teeth). It is caused by mutations in the *EDA* gene that encodes ectodysplasin. *EDA* gene is localized on chromosome X explaining the higher frequency of male patients. The EDA1 protein, acting through its receptor EDAR, is essential for the proper formation of skin appendages through the EDA pathway. The Tabby mice presented spontaneously with hypohidrotic ED related to *eda* mutations.

In 2003, Gaide and Schneider showed that the treatment of pregnant Tabby mice with a recombinant form of EDA, engineered to cross the placental barrier, permanently rescued the Tabby phenotype in the offspring. Notably, sweat glands can also be induced by EDA after birth. The developmental genetic defect was permanently corrected by short-term treatment with the recombinant protein [7].

In 2018, Schneider et al. [8] showed that the recombinant fusion protein, Fc-EDA, consisting of the receptor-binding domain of EDA and the Fc domain of human IgG1 administered intraamniotically to two affected human twins at gestational weeks 26 and 31 and to a single affected human fetus at gestational week 26 were able to permanently produce sweat normally and regulate their body temperature by the age of 3. The Fc-EDA provided in amniotic fluid must first enter the organism in a manner that is dependent on the neonatal Fc receptor, presumably through the gut, before it can act on developing EDA-dependent structures.

In the examples mentioned above, i.e., PROS syndrome and X-linked hypohidrotic ectodermal dysplasia, the therapeutic approaches were based on a deep understanding of the involved pathways. The respective genes were not corrected. In PROS syndrome, the PIK3-AKT-mTORC pathway was inhibited through the daily use of a small specific molecule. In X-linked hypohidrotic ED, the sweat development and function was permanently corrected through the direct trigger of the EDA pathway by a recombinant protein.

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8 Toenails: Where Orthopedics and Onychology Meet

Eckart Haneke

Onychomycoses are generally held to be the most frequent nail disorders. This was recently disputed when orthopedic abnormalities were recognized as being the cause of nail changes, in particular onycholysis. The authors had found that gait irregularities lead to nail changes and called this the "asymmetric gait nail unit syndrome (AGNUS)" [1, 2]. An analysis of toenail alterations in six different nail clinics in five countries confirmed that orthopedic problems associated with nail changes are at least as frequent as toenail mycoses although very often mistaken for fungal nail infections and other dermatoses (Figs. 8.1 and 8.2). Even in children, foot deformities can often be detected in association with nail alterations (Unpublished) [3].

The big toenail is the most common victim of orthopedic foot and toe abnormalities (Table 8.1). Although varying to an extreme extent even within the same individual, nail changes may look similar to other nail conditions, particularly onychomycoses and toenail psoriasis. Their pre-

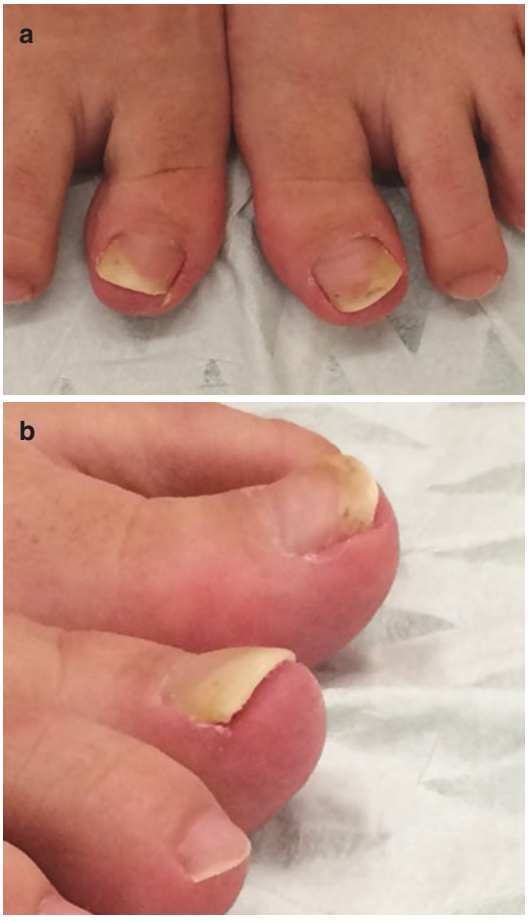

Fig. 8.1 Asymmetric gait nail unit syndrome in a 56-year-old patient with mild hallux valgus, hallux valgus interphalangeus, hallux erectus, and inward rotation of the big toe exhibiting distal onycholysis and nail bed hyperkeratosis. (**a**) Dorsal view. (**b**) Lateral view

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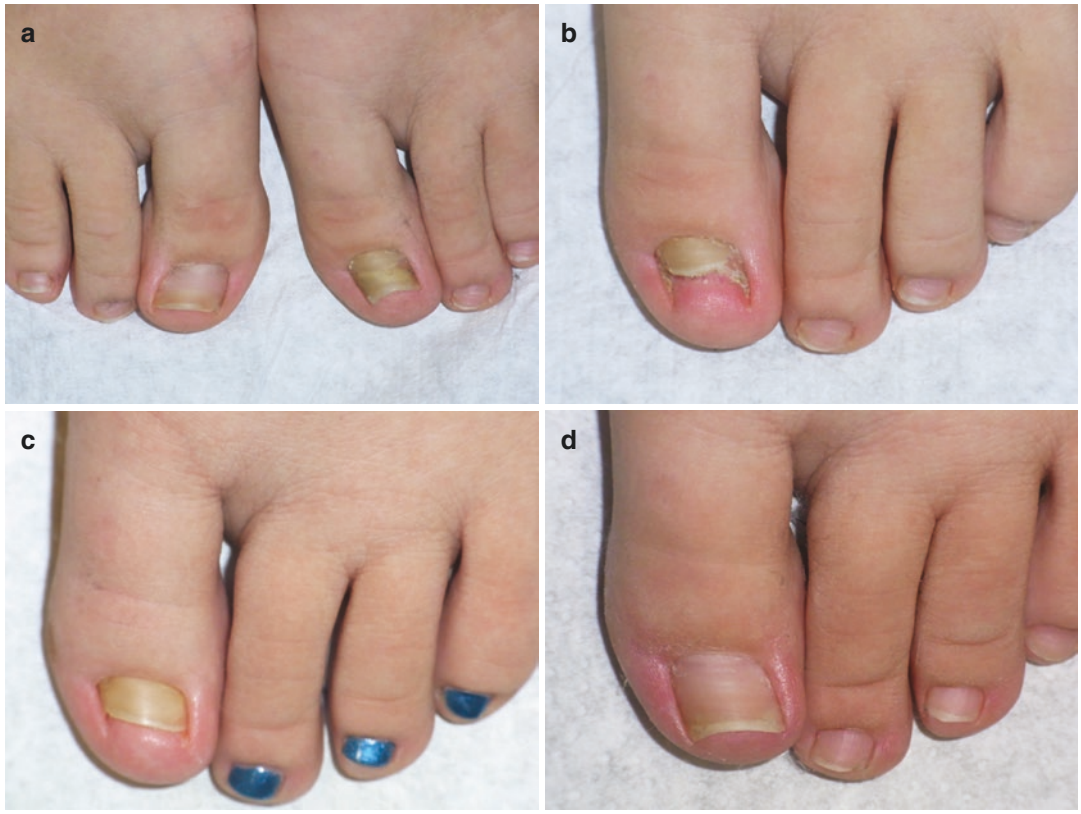

Fig. 8.2 Asymmetric gait nail unit syndrome in a 16-year-old girl. (**a**) Marked distal medial onycholysis associated with hallux valgus and hallux valgus interphalangeus. (**b**) Cutting the onycholytic nail away demonstrates a distal bulge in the front of the remaining nail. (**c**) After 5 months of consistent taping, nail growth is visibly improved. (**d**) One year later, a near-normal nail has regrown

Table 8.1 Minor and major orthopedic problems causing toenail abnormalities

Orthopedic problem	Big toenail	Lesser toenails
Hallux valgus	Onycholysis Subungual hyperkeratosis Subungual corn (heloma) Inward toe rotation Lateral deviation of big toe and toenails Retronychia Compression nails Pincer nails	Overriding toe Medial deviation of lesser toes and toenails Retronychia
Hallux erectus	Onycholysis Subungual hyperkeratosis Subungual corn	Often associated with hammertoe of the second toe
Hallux rigidus	Onycholysis	
Flat foot	Onycholysis	
Splayfoot	Onycholysis Inward rotation of big toe	Outward rotation of the little toe
Double little toenail [19]		Broad little toenail often mistaken for corn. Tends to catch stockings when pronounced
Short distal phalanx	Upward growing of big toenail	Increased longitudinal curvature of lesser toenails => parrot nails
Age-related foot deformation	Onycholysis, malposition, thickening, onychogryphosis	Onycholysis, malposition, thickening, onychogryphosis
Wide base of the distal toe phalanx [20, 21]	Pincer nails, usually associated with lateral deviation of the distal phalanx and the nail	Pincer nails, usually associated with medial deviation of the distal phalanx and the nail

cise differential diagnosis is of paramount importance to institute a correct treatment and to avoid lengthy, expensive, and potentially risky therapies [4].

Hallux Valgus

Bunion deformity is an extremely common disorder affecting a high percentage of the population with female predominance. It is an autosomal dominant condition with a positive family history in 90% of the cases [5]. The genetic component is said to be stronger when the hallux valgus occurs in younger persons [6]. In a community-based study of 600 elderly Bostoners, 52% of women and 25% of men had hallux valgus, which was defined as an angular deviation >15° of the big toe in relation to the first metatarsal bone toward the lesser toes. Theories as to its etiology abound: Several factors of hallux valgus development have been reported to be associated with structural factors, sex, age, BMI, foot pain, pes planus, and footwear. Among the structural factors are also metatarsal length, metatarsal head shape, first ray hypermobility, and hind-foot pronation. Clinically, hallux valgus is more frequently observed in women and more prevalent in the elderly. An association with increased BMI, foot pain, and pes planus was also seen. The prevalence of hallux valgus is much higher in persons wearing shoes than those with unshoed feet, and shoe types may be important in the development of hallux valgus [7]. However, the claim that high-heeled shoes are the main reason for the female predominance is certainly not true. Hallux valgus is said to be extremely rare in little children [8–10], a statement that we *cannot* confirm. In contrast, systematic X-ray examinations in infants and little children have shown a medial deviation of the first metatarsal bone in relation to the second one associated with an oblique joint line of the first cuneiform-metatarsal joint. This is, curiously, not mentioned in the extensive literature on hallux valgus. It is also evident that hallux valgus gets worse with age as it is a self-aggravating condition since both the flexor and the extensor tendons pull and increase the angle

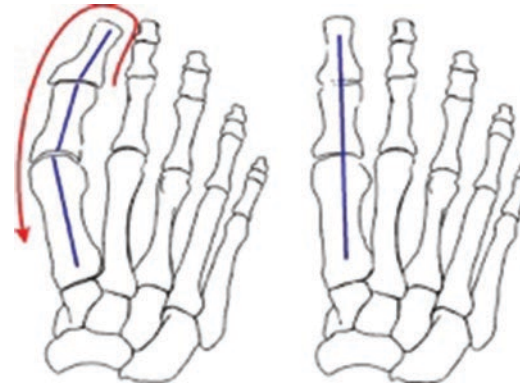

Fig. 8.3 Left: Hallux valgus starts at the joint between os cuneiforme I and os metatarsale I: the joint line is oblique. The blue lines show the arc formation of the first ray. The red line indicates the action of taping. Right: Ideal straight position of metatarsale I – basal and distal phalanx of the big toe

of the arch (Fig. 8.3). Although taping cannot address the oblique os cuneiforme I–os metatarsale I joint space, it is able to correct the metatarsophalangeal and the interphalangeal joints. Long-term pressure leads to bone reduction and long-term tension to bone apposition or growth, respectively, which is the principle of taping in hallux valgus treatment.

The nails in hallux valgus are often thickened, nontransparent, and partially onycholytic, and there is a nail bed hyperkeratosis; this appearance is frequently confused with onychomycosis. An acquired asymmetric lateral nail deviation may develop. In severe cases, an onychogryphosis may occur. This abnormality is also prone to development of chronic retronychia (Fig. 8.4).

Hallux valgus interphalangeus is defined as a lateral deviation of the long axis of the distal phalanx from that of the first phalanx. Together with the common hallux valgus, it forms an arch of the first ray that tends to self-aggravate due to foot activities with pull on the flexor and extensor tendons of the hallux. On X-ray films, an asymmetric distal phalanx is seen with an exaggerated medial condyle in adults and an asymmetric epiphysis of the distal phalanx in children (Fig. 8.5). This is virtually always observed in the hereditary type of pincer nails [20, 21]. Again, conservative treatment is by taping.

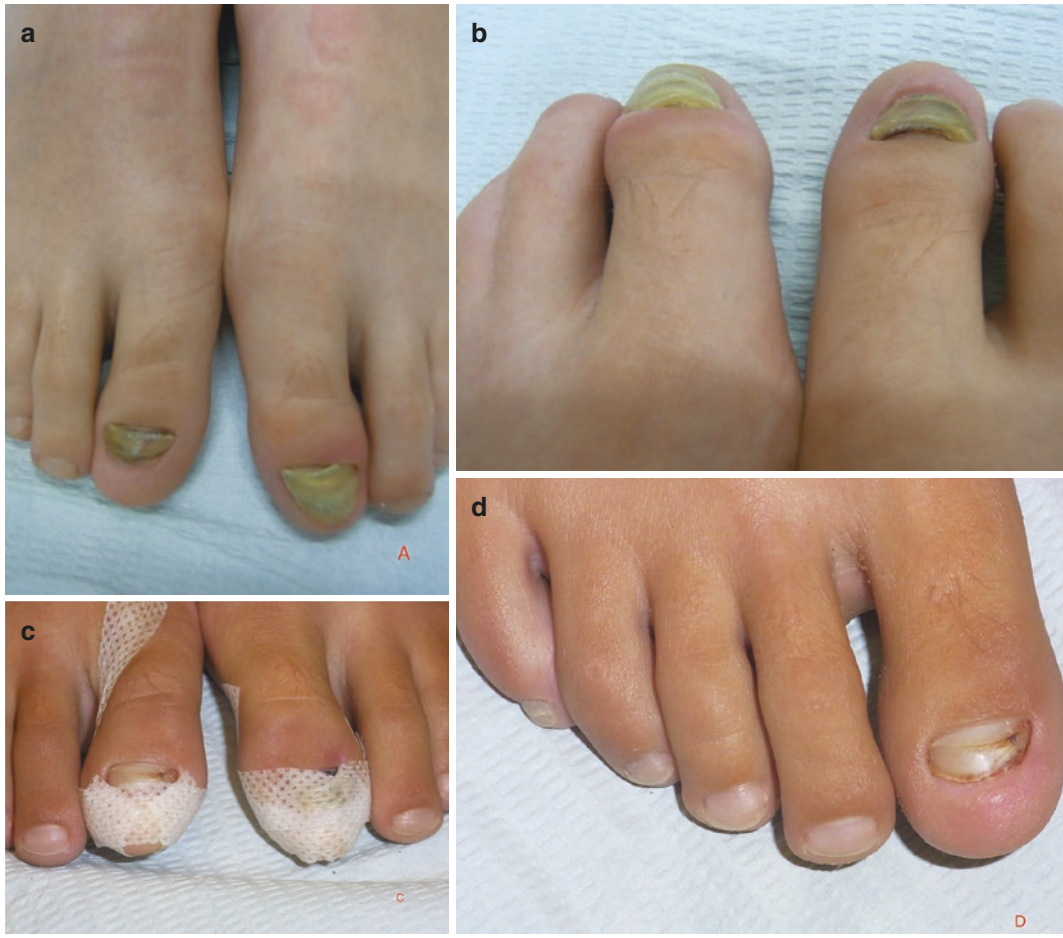

Fig. 8.4 Chronic retronychia in a 12-year-old female patient with hallux valgus and mild hallux valgus interphalangeus. (**a**) Dorsal view. (**b**) View from proximal. (**c**) Taping of the toe. (**d**) After 4 months of taping

Splayfoot

Hallux valgus is almost always associated with a splayfoot. Nail changes may be similar, though not so pronounced. Inward rotation of the big toe and outward rotation of the little toe are associated. The little toe may be rotated to a degree that it stands vertical, which may cause a parungual callus causing pain while walking. This is even more pronounced in case of a double little toenail (Fig. 8.7).

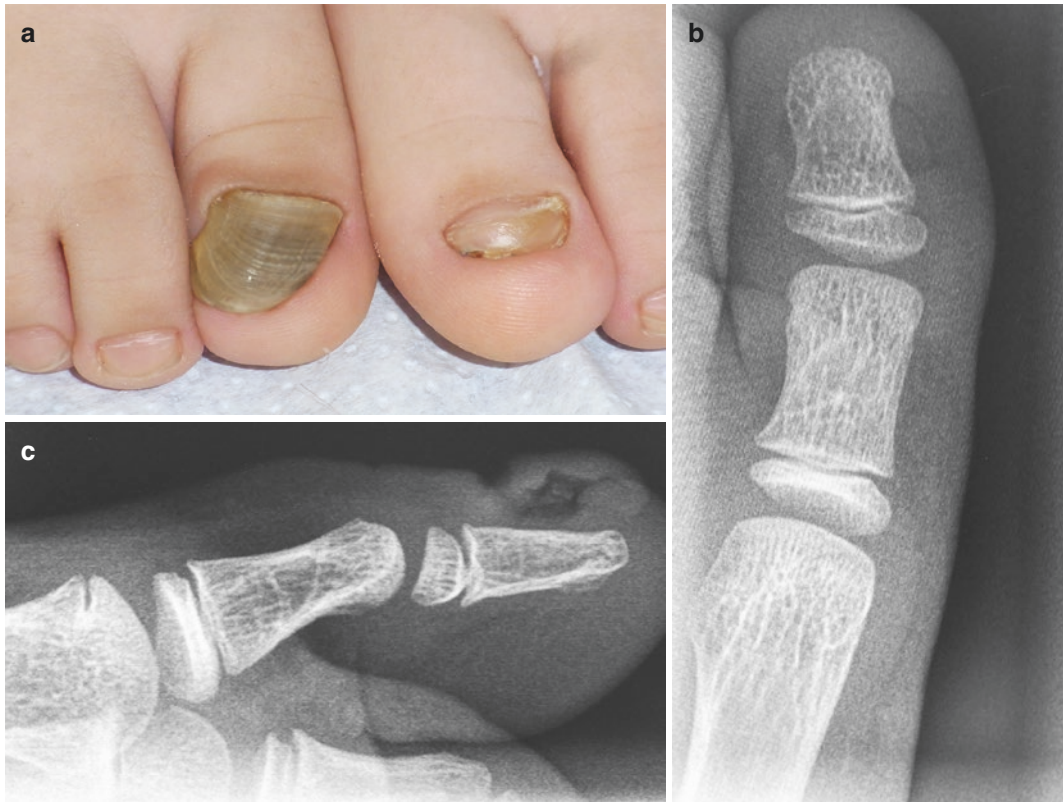

Fig. 8.5 A 5-year-old girl with congenital malalignment and hallux valgus interphalangeus (**a**). The X-ray film of the right toe shows an asymmetric wedge-shaped epiphysis of the distal phalanx of the great toe (**b**). Also, the lateral X-ray demonstrates an asymmetric epiphysis explaining the upward direction of the distal phalanx. The nail is bridging a deeply sunk-in nail bed, and there is a distal bulge (**c**)

Pes Planus

Flat foot is also very common and usually combined with splayfoot. Nail changes are virtually identical.

Hallux Erectus

Hyperextension of the hallux results in a condition called hallux erectus. A statistically significant correlation between hallux interphalangeal joint hyperextension and first metatarsophalangeal joint pain was found ($r = 0.78$, $p = 0.01$) [8]. The dorsal overextension leads to the friction of the free nail margin at the shoe box and may consequently cause distal subungual hyperkeratosis that is often confounded with distal subungual onycholysis (Fig. 8.6). Clinically, the extensor hallucis tendon stands out as an elevated band. Dermatologic treatment is by taping the hallux down in a slightly overcorrected position: A tape of 2 cm width is fixed on the nail and led around the tip of the toe to its pulp and with some tension

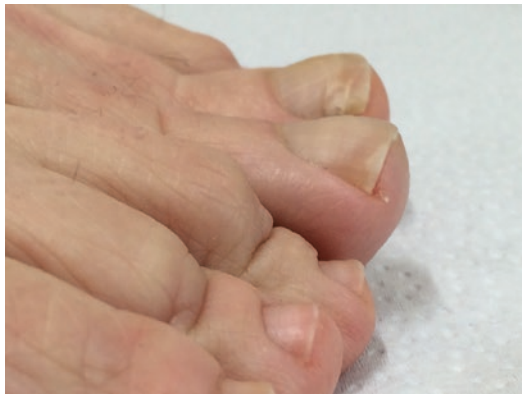

Fig. 8.6 Hallux erectus with distal onycholysis

over the plantar surface of the basal phalanx to the ball of the foot. To keep the tape in place, another tape is lightly fixed around approximately 270° of the basal phalanx like a holster. With time, the patients learn not to pull the big toe upward.

Hallux Rigidus

Hallux rigidus is degenerative arthritis of the first metatarsophalangeal joint. With 2.5% of all persons over 50 years suffering from hallux rigidus, it is said to be the most frequent arthritic condition of the foot [9]. Its progression is associated with pain and limited motion. Depending on its severity, nail changes vary from mild onycholysis, to subungual hyperkeratosis, to onychogryphosis.

Double Little Toenail

This tiny abnormality of the fifth toenail is quite common, though very often overlooked [10, 19]. It is seen in all races and is apparently autosomal dominant [10, 19]. The nail may be obviously doubled or be just wider with a longitudinal split or only an indentation (Fig. 8.7). The reason is a small bone spike at the disto-lateral side of the distal phalanx that gives rise to an accessory nail anlage. This can be seen in good radiographs although they are difficult to obtain. The double nail of the little toe may become symptomatic in patients with splayfoot and pes planus when the fifth toe rotates outward and stands vertical. This is felt like a clavus with which it is very often confounded. Treatment is by surgical resection of the accessory nail segment or by chemocautery of the accessory matrix portion [10, 19].

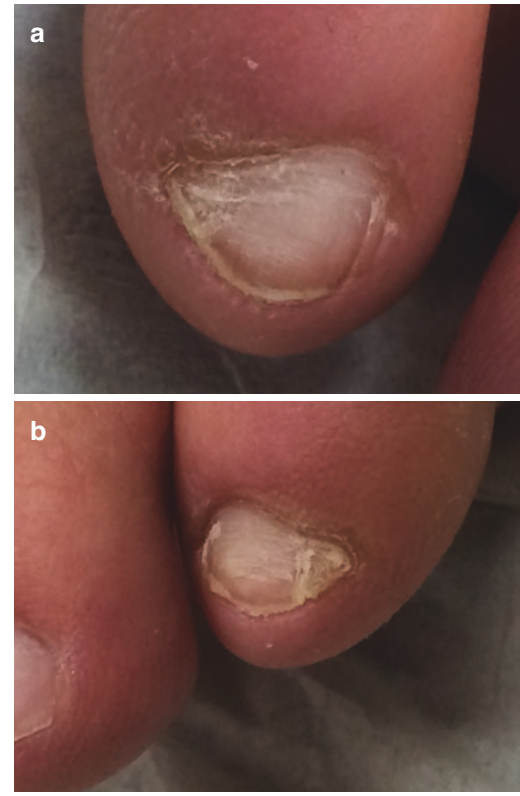

Fig. 8.7 Double little toenail. The right fifth nail exhibits just a shallow longitudinal depression (**a**), whereas the left one shows a longitudinal split running till the cuticle and clearly delineating the accessory nail (**b**)

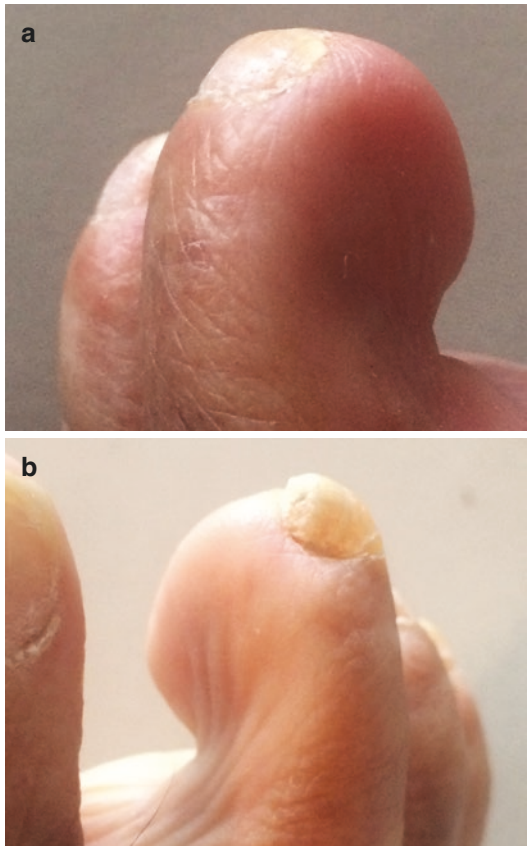

Fig. 8.8 Short distal phalanx of the second toes with longitudinal overcurvature of the nail. (**a**) Left third toe. (**b**) Right third toe

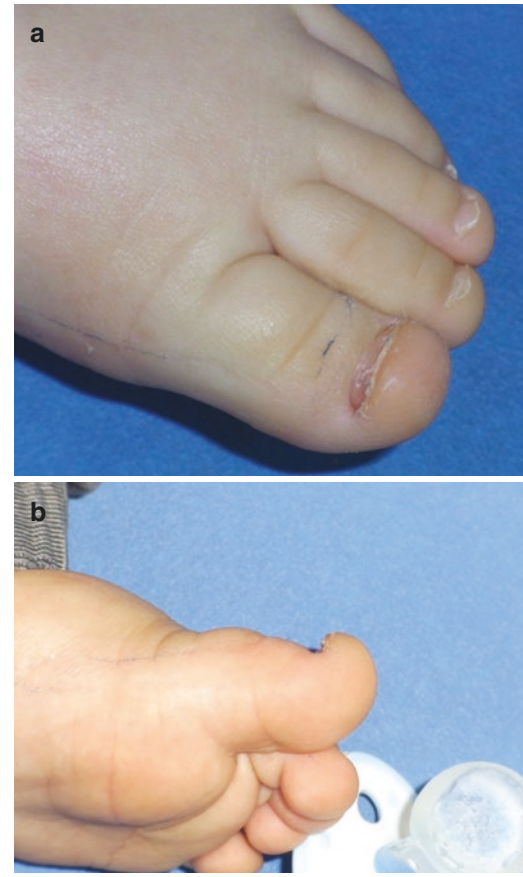

Fig. 8.9 Upward distortion of the big toenail in an abnormally short distal phalanx. (**a**) Dorsal view. (**b**) Lateral view

Short Distal Phalanx

The distal phalanx of the toes may be abnormally short although the nail bed is of normal length. This leads to the lack of support of the distal nail bed which is pulled plantarly and causes a pronounced longitudinal curvature of the nail in the sense of a parrot beak nail (Fig. 8.8). The nail may press into the pulp and cause a callus similar to what is seen in a hammertoe. Sometimes, there may be a central split in the distal nail plate. An abnormally short distal phalanx of the big toe in little children may lead to upward distortion of the nail as the pulp of the toe is dislodged dorsally during gait (Fig. 8.9).

Age-Related Foot Deformation

More than 40% of the population has foot problems and the prevalence increases with age. They are usually painful and impede walking and many sports activities. All types of nail changes described above may develop.

Wide Base of the Distal Toe Phalanx

According to our investigations, a wide base of the distal phalanx of the big toes is always seen in the symmetrical form of pincer nails [5, 6].

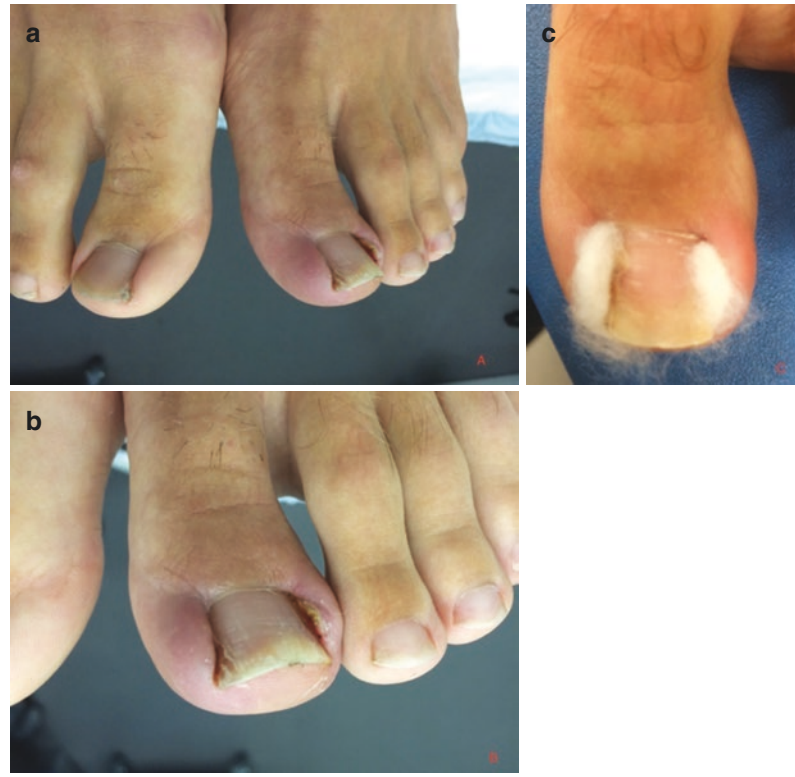

Fig. 8.10 Moderate overcurvature of the big toenails in a 17-year-old male patient with mild hallux valgus and hallux valgus interphalangeus. (**a**) Dorsal view of both sides. (**b**) Left toenail with painful ingrowing of the lateral nail edges. (**c**) Immediate pain relief by insertion of a wisp of cotton under the lateral nail edges

The terminal phalanx is asymmetrical and shows laterally, whereas affected lesser toes are medially deviated (Figure). The basal condyli are increased with a bigger one on the medial side, which is easily felt with sliding palpation. With time, this develops into a hooklike shape possibly representing the insertion of the medial interosseous ligament. The matrix horns are located here, which results in a widening of the natural curvature of the hallux nail proximally that now compensatorily curves in more distally [20, 21]. The result is the typical nail overcurvature that is sometimes more than 360° at the free nail margin. In the beginning, when the lateral nail margins are vertical, they may press into the lateral nail sulcus which causes pain and may induce an ingrowing nail in younger persons (Fig. 8.10) and in older persons a hyperkeratosis in the nail sulcus called onychophosis (Fig. 8.11). In addition to the pronounced condyli at the base of the distal phalanx, a small osteophyte is often seen on lateral-view radiographs; they develop from traction by the elevated distal nail bed.

Treatment of pincer nails depends on the severity and symptoms. In mild cases, orthonyx therapy with elastic steel braces, shape memory alloy nail clips, plastic strips, and taping may alleviate pincer nails [11]; however, as they do not attack the underlying bone alterations, recurrences are very frequent and appear quick. As the medial and lateral condyli cannot be removed without risking to damage the lateral ligaments and destabilize the joint, the lateral matrix horns on which they act have to be removed. This is best done by avulsing a medial strip of the nail plate and selectively remove the matrix horn, either by scalpel dissection or chemocautery with phenol, trichloroacetic acid 85%, or sodium hydroxide 10%. In case of severe nail bed deformation, a nail bed plasty is recommended [20, 21].

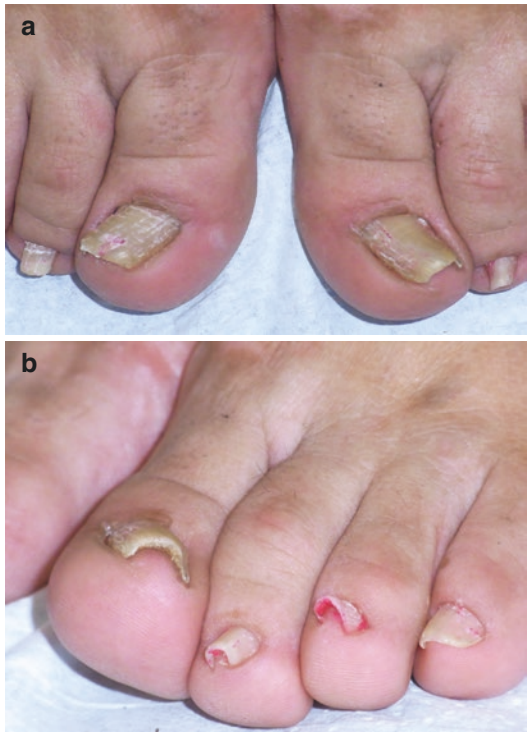

Fig. 8.11 Pincer nails in a 55-year-old female patient with marked lateral deviation of the distal big toe phalanges and medial deviation of the distal phalanges of the affected lesser toes. (**a**) Dorsal view. (**b**) Frontal view

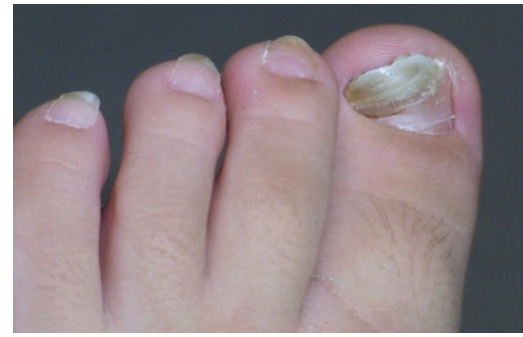

Fig. 8.12 Congenital malalignment in a 5-year-old boy. There is a mild interphalangeal valgus position of the fourth toe with mild medial nail deviation

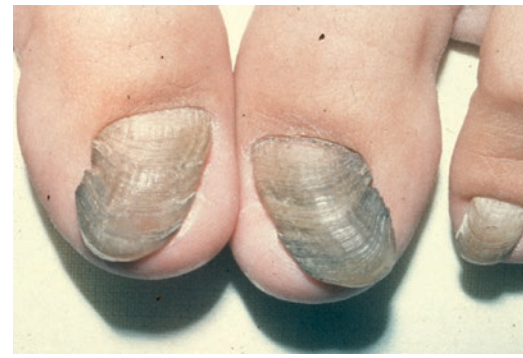

Fig. 8.13 Untreated congenital malalignment of the big toenails of a 12-year-old girl

Inborn Nail Abnormalities in Children with Bone Changes

Congenital dystrophy of the great toenail was described in 1978 [12] and renamed congenital malalignment of the great toenail in 1979 as it was recognized to be associated with a lateral deviation of the nail's long axis [13]. The condition is characterized by a thickened, discolored, malformed triangular nail with a lateral deviation of its long axis. Its surface is oyster shell-like with Beau's lines that are the result of horizontal splits in the matrix from compression in the longitudinal axis, a mechanism exactly identical to that of retronychia. The transverse ridges are usually closer to each other on the lateral nail plate indicating a curvature in the long axis of the nail, which might be due to the higher proliferation of the medial in relation to the lateral matrix horn (Figs. 8.12 and 8.13). The nail margins press into the soft tissue leaving pressure marks. We have found severe onycholysis in all fully developed cases (Fig. 8.14), which is apparently the most important prognostic factor. Onycholysis is also the reason for the extreme shortening of the nail bed and heaped-up tissue in front of the nail, which is the cause of the worsening by minor trauma [14]. X-ray examinations have shown a mild to moderate hallux valgus formation, mostly as a hallux valgus interphalangeus (Fig. 8.15) [15]. Another group postulated that a hypertrophy of the latero-posterior ligament inserting at the matrix horn would pull the matrix proxi-

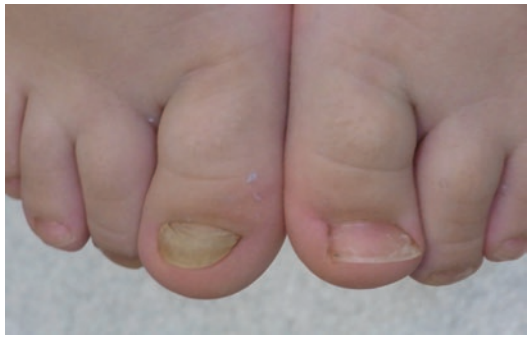

Fig. 8.14 A 5-year-old girl with congenital malalignment of the hallux nails; the right nail is onycholytic and demonstrates all features of the disease, whereas the left nail is not onycholytic and only shows a trapezoid nail

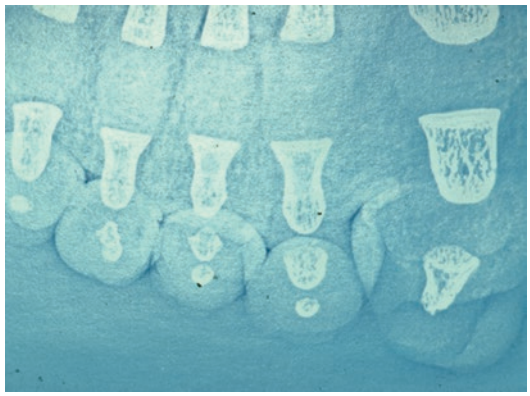

Fig. 8.15 Radiograph of the forefoot of a 1-year-old girl with congenital malalignment of the big toenail

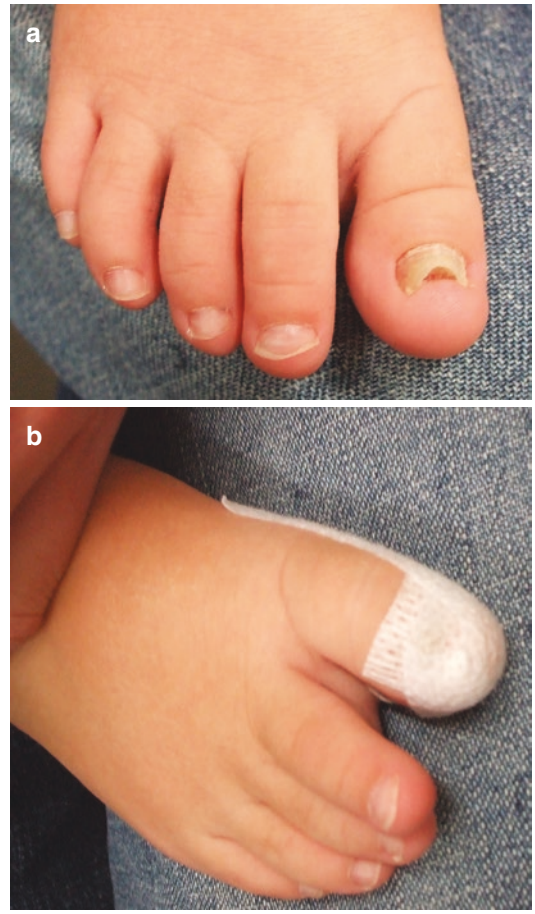

Fig. 8.16 Congenital overcurvature of the right hallux nail in a 4-year-old boy with a mild hallux valgus (**a**). Taping of the right big toe leads to a better toe position as seen at the interdigital space between toes 1 and 2 (**b**)

mally resulting in an oblique direction of the nail growth [16]. This would also explain the bulge over the lateral matrix horn.

Whereas some authors have seen spontaneous resolution in almost half of their cases [17], our experience is much less favorable. The surgical correction of the long axis of the entire nail unit devised in 1983 requires dissection of the entire nail unit beyond the proximal matrix and is usually successful if done before the age of 2 years; the later the surgery, the less the results are satisfying [3]. Due to the modest results of surgery, we have performed taping in infants and children to correct the hallux valgus and hallux valgus interphalangeus to correct the bone position. A tape is fixed at the lateral side of the big toe and carried around its tip along the toe's medial side to the midfoot with tension. This immediately shows a better toe axis. The tape is applied to correct the direction of the phalanges (Fig. 8.16), and another tape is applied on the maldirected nail plate to pull it medially. Further, as there is no counterpressure for the toe pulp during gait by the onycholytic nail, a distal bulge develops, and the nail bed shrinks. The success rate is better than surgery provided the taping is done correctly and consistently. The treatment duration in infants is usually 1 year and increases with the age of the patient. When the feet are sweaty, particularly in summer, the skin may be painted with an alcoholic extract of the resin of the mastic tree (Mastisol®), which renders the skin much stickier. Untreated congenital malalignment – if not resolving spontaneously – leads to very unsightly

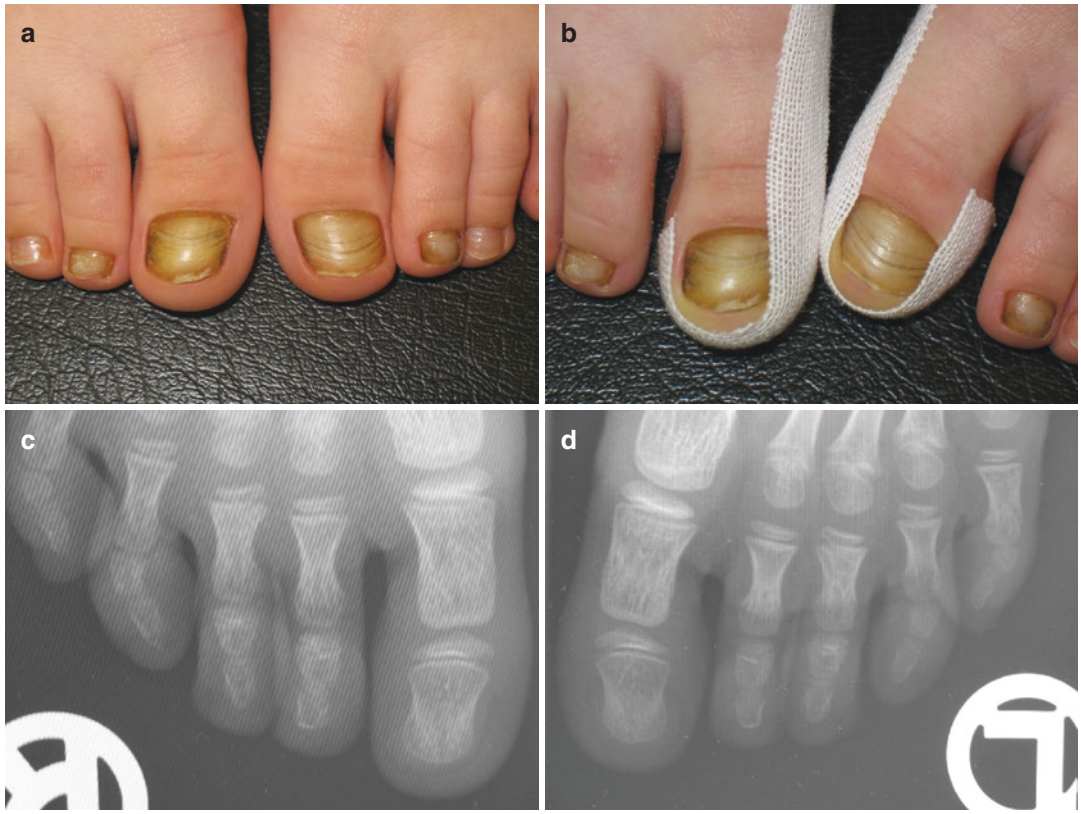

Fig. 8.17 Hallux valgus interphalangeus with severe onycholysis as evidenced by the yellow nail discoloration and multiple transverse lines. (**a**) Before taping. (**b**) With taping. (**c**,**d**) X-ray films show the hallux valgus interphalangeus and the wedge shape of the distal phalanx epiphysis

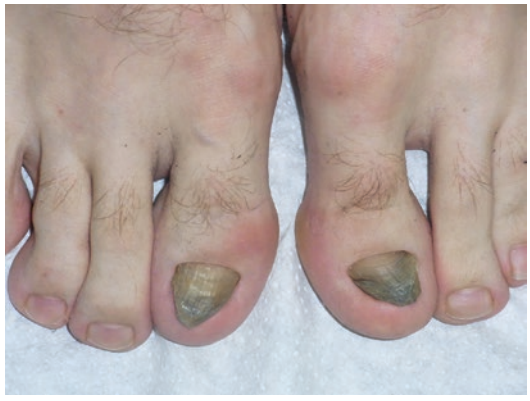

Fig. 8.18 Congenital malalignment of the big toenails in a 26-year-old man with hallux valgus and hallux valgus interphalangeus

nails, and many teenagers and young adults are then embarrassed by their ugly nails (Figs. 8.17 and 8.18).

Congenital malalignment is also seen as a late-onset condition [18]. This is not uncommon and, in our experience, virtually always associated with a pronounced hallux valgus interphalangeus. We postulate that due to the bone malposition, there is an unphysiological strain and stress on the nail leading to onycholysis that progresses and is followed by disappearance of the nail bed, which gives support to the nail plate. The lack of nail plate support allows movements with shearing forces that result in horizontal splits between the nail and matrix. A trauma is usually remembered as the precipitating event. Finally, a clinical pattern develops that is indistinguishable from the congenital form. Treatment of adults with neglected congenital malalignment is usually unsuccessful. Total matrix phenolization is then cosmetically and functionally superior to the thick discolored nail that is often painful and impedes normal gait and sports activities (Figs. 8.19 and 8.20).

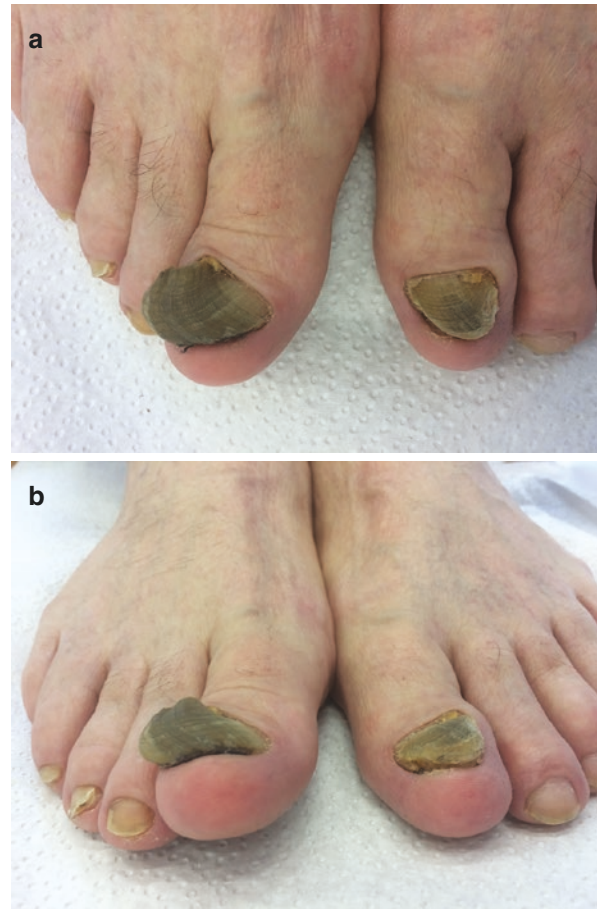

Fig. 8.19 Congenital malalignment of the big toenails in a 35-year-old female patient. (**a**) Dorsal view; note the bulge of the lateral matrix horn of the right toe. (**b**) Frontal view showing a mild hyperextension of the right hallux. Probing shows that there is virtually no nail bed left

Other big toenail alterations in newborns and infants are represented by upward nail growth and nail overcurvature. All these toenail dystrophies have an asymmetric epiphysis in common that does not exhibit the ideal lenticular shape but more a wedge shape. The base of this wedge is medial in case of lateral deviation and plantar in upward growing nails (Fig. 8.21).

Medial deviation of a lesser toenail is occasionally seen. It presents as a thick, curved discolored onycholytic nail mimicking onychogryphosis.

Overcurvature of the hallux nail is sometimes seen in infants and preschool children. It is very often associated with lateral nail deviation (Figs. 8.22 and 8.23).

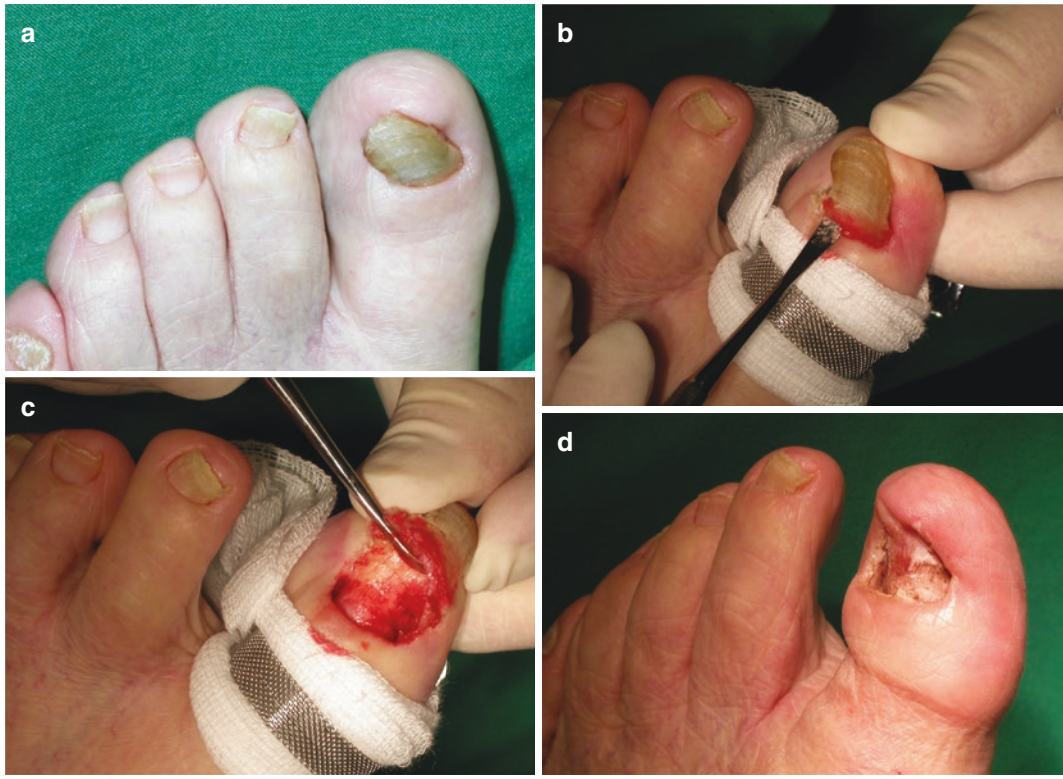

Fig. 8.20 Neglected congenital malalignment of the left big toenail in a 62-year-old woman causing pain. There is a lateral deviation of the hallux and a medial deviation of the second toenail pointing at a complex condition. (**a**) Almost complete onycholytic discolored nail. (**b**) Proximal nail avulsion. (**c**) The nail plate is elevated from proximal showing a normal matrix length. (**d**) Immediately after phenolization of the entire matrix, an extremely short nail bed is seen with a very big distal hump due to lack of counterpressure during gait

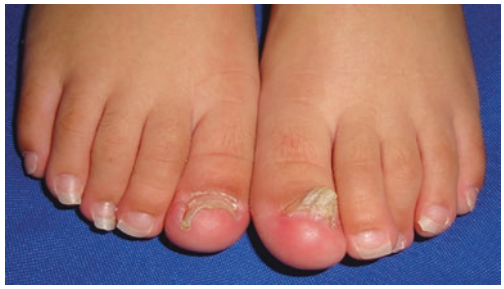

Fig. 8.21 Overcurvature of the right hallux nail and upward growth of the left nail (Courtesy Dr. Patricia Chang, Guatemala)

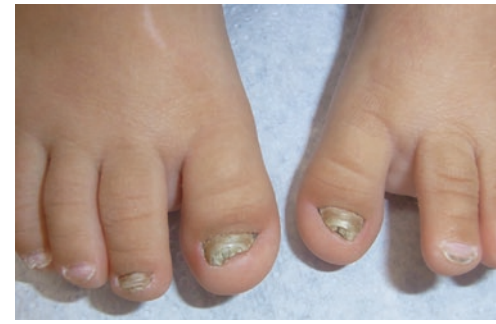

Fig. 8.22 Congenital nail dystrophy with lateral deviation and overcurvature due to hallux valgus interphalangeus

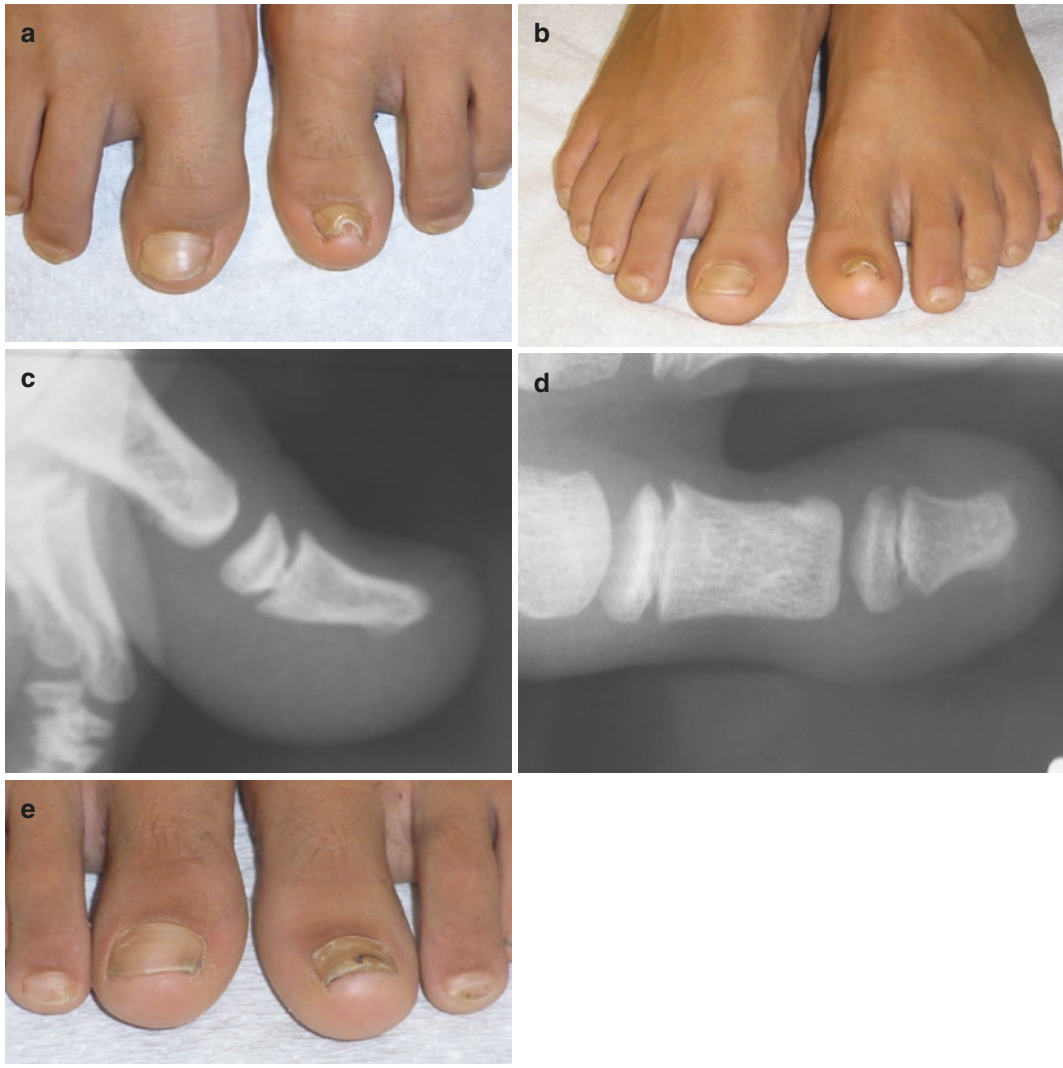

Fig. 8.23 An 8-year-old boy with congenital unilateral upward growing and overcurved big toenail. (**a**) Dorsal view. (**b**) Frontal view. (**c**) Lateral-view X-ray demonstrating the slightly asymmetric distal epiphysis and the upward direction of the distal phalanx. (**d**) X-ray dorsoplantar view showing the asymmetric epiphysis of the distal phalanx. (**e**) Same patient at age 11 after 2 years of taping

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9 Recent Advances in Nails in Systemic Disease

Mark Holzberg

The nail is known as the "window" to the human body. In classic physical diagnosis in medicine, changes in the nails were often used as clues to systemic disease. With modern technology, these changes are less relied upon, but they can be very helpful in bedside diagnosis and in pointing the clinician to the underlying associated systemic disease state.

This chapter reviews recent advances in the literature which associate nail changes with systemic disease. Discussion will group these changes by the associated anatomic position in the nail apparatus.

Proximal Nail Fold

Color

Capillary changes in the proximal nail fold are most often associated with collagen vascular disease. Two patterns of capillary nail fold telangiectasias can be best visualized with magnification using a dermatoscope or an ophthalmoscope with a drop of oil over the proximal nail fold: (1) a systemic lupus (SLE) pattern involving tortuous meandering capillary loops and (2) a scleroderma-dermatomyositis pattern characterized by capillary dilation and avascular areas. Ragged cuticles and nail fold infarcts can also be associated findings in the proximal nail fold. In addition to SLE, scleroderma, dermatomyositis, and mixed connective tissue disease, nail fold capillary telangiectasias have been associated with Sjogren's syndrome, rheumatoid arthritis, inflammatory bowel disease, Henoch-Schönlein purpura, diabetes, cryoglobulinemia, cystic fibrosis, and schizophrenia [1]. In a recent retrospective article examining 176 patients, measurable capillaroscopic changes consisting of ischemic areas and wider proximal nail fold capillary loops were found in both limited cutaneous and diffuse systemic sclerosis [2]. Capillary microscopy has been of value in the diagnosis of hereditary hemorrhagic telangiectasia [3].

Bywaters lesions are purpuric lesions on the fingers in patients with rheumatoid arthritis and are a sign of leukocytoclastic vasculitis (Fig. 9.1). A recent case report of a 79-year-old Finnish woman with a 40-year history of rheumatoid arthritis describes biopsy-proven Bywaters lesions of the nail folds, fingers, and palms confirming leukocytoclastic vasculitis [4]. The authors comment that rheumatoid vasculitis rarely occurs in rheumatoid arthritis patients (<1%) and usually occurs late in the disease. When an isolated finding, the prognosis is considered favorable.

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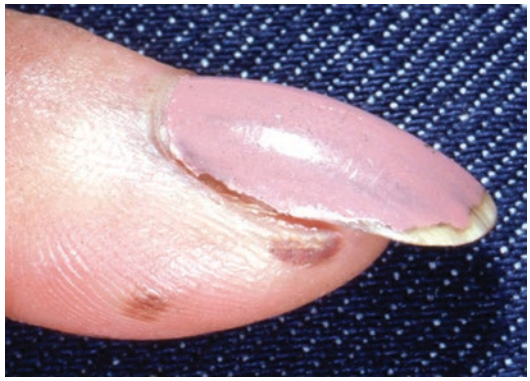

Fig. 9.1 Bywaters lesions

Matrix

Color

When red lunulae are noted in just one digit, the clinician should consider a dermal tumor, but when the lunulae in multiple nails are involved, one should consider a more generalized association [5]. Red lunulae are associated with a number of conditions including cardiac failure and alopecia areata [6]. The condition has been reported in cirrhosis, gastrointestinal disorders, Hodgkin's disease, osteoarthritis, pneumonia, polymyalgia rheumatica, lichen planus, psoriasis, renal and respiratory diseases, rheumatoid arthritis, thyroid disease, and tuberculosis [1]. Morrissey et al. reported a case in which the red lunula was biopsied and found histologically to be due to an increased density of benign-appearing and mildly dilated vascular channels present in the superficial papillary dermis of the nail matrix [6]. Wollina et al. reported red lunulae in lupus erythematosus and noted it was most common in all fingernails and in 19.6% of lupus erythematosus patients examined [7].

Roest et al. reported that nail changes occur in up to 64% of alopecia areata patients with pitting (29.7%) being most frequent followed by trachyonychia (18.0%) and red spots in the lunula (5.1%) [8]. The presence of these nail changes reflects the severity of the disease, with red spots in the lunula being the best predictor for severe alopecia.

Shape

Lunula shape changes in response to certain systemic disease states [1]. The lunula is absent in patients with certain porphyrias and renal disease, especially patients on hemodialysis and post-renal transplantation. Despite being associated with habit tic deformity nails, macrolunulae are also associated with hyperthyroidism and leprosy patients. Triangular lunulae are the hallmark of nail-patella syndrome.

Nail Bed

Color

In 1954, Richard Terry published a report documenting a nail change consisting of a ground-glass-like opacity of almost the entire nail bed except for a distal 1–2 mm pink band (Fig. 9.2) and associated it with 82 or 100 cirrhosis patients [9]. Holzberg and Walker examined 512 consecutive hospitalized patients and found Terry's nail in 25.2% but with slightly modified criteria [10]. Nails with a 0.5–3.0 mm distal pink nail

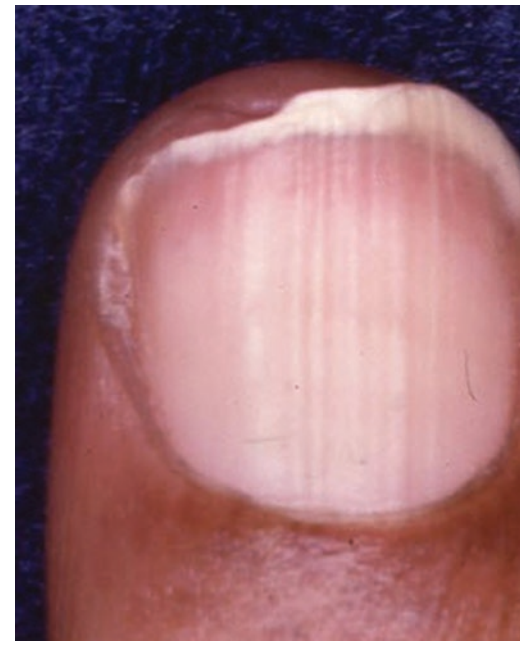

Fig. 9.2 Terry's nail

bed band and proximal pallor were associated with cirrhosis but further associated with chronic congestive heart failure and adult-onset diabetes especially in older patients. Terry hinted at additional associations with pulmonary tuberculosis, rheumatoid arthritis, convalescent hepatitis, disseminated sclerosis, and carcinoma [9]. Terry's nails have also been reported in reactive arthritis, renal transplant patients, POEMS syndrome, leprosy, and inflammatory bowel disease, but it is cirrhosis that appears to be the most reliable physical associated sign [11]. Nelson et al. noted that clinicians observing Terry's nails in an adult outpatient setting should strongly consider the possibility of cirrhosis, a finding they found as strongly associated [12].

Both Terry's nails and the half-and-half nail exhibit a distal pink to brown band and proximal pallor, and both can be seen in completely normal individuals as a normal variant [13]. The half-and-half nail, or Lindsay's nail, however presents with a distal band covering 20–60% of the distal nail bed (Fig. 9.3). First described by Bean in azotemia [14], Lindsay found the nail change in 25 of 1500 consecutive hospital admissions and associated it most commonly with azotemia of chronic renal failure (84%) and less commonly with urinary casts and a low creatinine clearance [15]. The nail change has also been associated with Behcet's disease, cirrhosis, Crohn's disease, HIV, pellagra, citrullinemia, and zinc deficiency [1]. A recent report from Tunisia documents the half-and-half nail with end-stage renal disease and chronic dialysis in 13.5% of patients [16]. In an Israeli case-control study of 73 chronic renal failure patients and 77 patients undergoing hemodialysis, the incidence of half-and-half nails was 12.3% and 16.9%, respectively [17]. The association of half-and-half nail and Crohn's disease is an interesting one. In one report, the association may be due to an associated zinc deficiency [18], but in yet another case report, zinc levels were normal [19]. Adding to the literature of androgen and chemotherapeutic agent drug-induced half-and-half nails [1], the half-and-half nail was recently reported in a seven-year-old girl after 1 month of chemotherapy with oral methotrexate and 6-mercaptopurine for pre-B acute lymphoblastic leukemia [20].

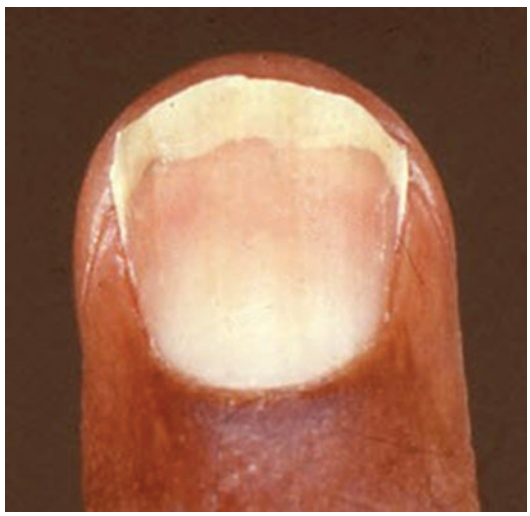

Fig. 9.3 Half-and-half nail

In addition to the half-and-half nail, there are a constellation of nail findings associated with renal failure. Other nail changes commonly seen in renal failure are absent lunula and onycholysis and, less frequently, brittle nails, Beau's lines, clubbing, longitudinal ridging, onychomycosis, subungual hyperkeratosis, koilonychia, total leukonychia, pitting, pincer nail deformity, chromonychia, nail dystrophy, melanonychia, leukonychia, longitudinal striae, trachyonychia, koilonychia, and Muehrcke's lines [21]. In patients with chronic renal failure undergoing hemodialysis, the half-and-half nail is the most common nail finding, but other findings in decreasing order are absent lunula, onycholysis, brittle nail, Beau's lines, clubbing, longitudinal ridging, onychomycosis, subungual hyperkeratosis, koilonychia, total leukonychia, splinter hemorrhage, pitting, and pincer nail deformity [22].

In 1956, Muehrcke described two transverse bands of pallor in the nail beds (Fig. 9.4) of patients with hypoalbuminemia and an albumin of <2.2 g/dl [23]. However, hypoalbuminemia is not a reliable finding in patients with Muehrcke's lines [1]. These bands of pallor can be seen in nephrotic syndrome, glomerulonephritis, liver disease, malnutrition, acrodermatitis enteropathica, and chemotherapy [1]. One case report emphasized that perhaps the unifying condition for all associated

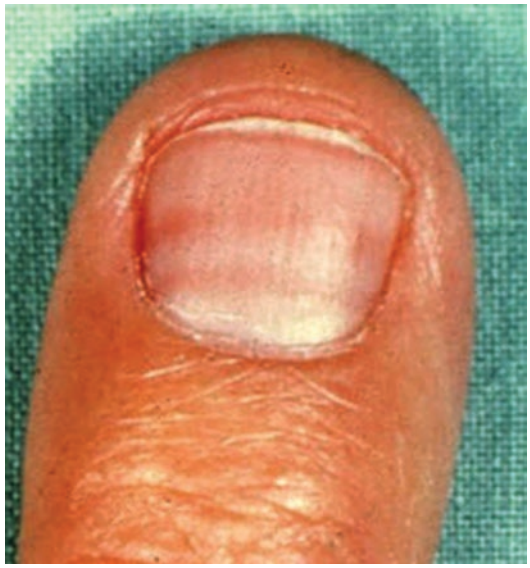

Fig. 9.4 Muehrcke's lines

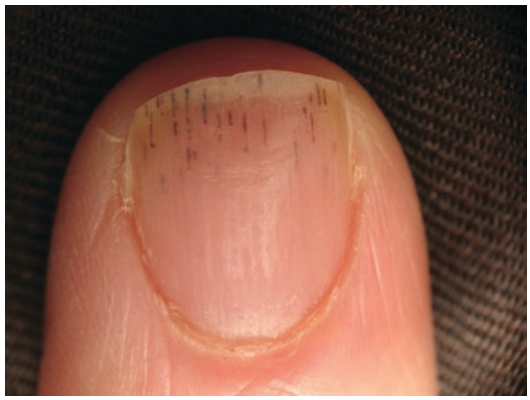

Fig. 9.5 Splinter hemorrhages

disease states in patients with Muehrcke's lines might be a severe chronic and catabolic systemic disease state [24].

Vascular injury interrupts the parallel vasculature of the nail bed and causes a linear hemorrhage clinically apparent as a splinter hemorrhage (Fig. 9.5). These tiny hemorrhages are reddish usually asymptomatic linear streaks under the nail plate usually at the distal third of the nail bed. First observed by Sir Thomas Horder in 1920, these small linear hemorrhages in the nail bed were first noted in a patient with bacterial endocarditis but are now known to be recognized and associated with a variety of systemic disease states including vasculitis, connective tissue disease, and antiphospholipid syndrome; infections such as chronic meningococcemia; exposure to high altitude; trauma; activities of daily living; and many other conditions [25]. Other causes include cardiovascular, gastrointestinal, renal, neurologic, endocrine, and drug-related associations [1]. To many, splinter hemorrhages still remain an invaluable physical sign and clue that lead to early recognition, diagnosis, and treatment of a variety of significant health issues, especially in association with emboli, Osler's nodes, Janeway lesions, Bowman lesions of the eye, Roth spots, petechiae, and clubbing [26]. In endocarditis, splinter hemorrhages are usually found in infectious endocarditis. But a recent report by Usui et al. associates splinter hemorrhages and Janeway lesions with a noninfectious eosinophilic endocarditis, improving as the endocarditis improved [27]. In another recent article of a hypereosinophilc vasculitis associated with Raynaud's phenomenon, digital ischemia, and vasculitic rash, a 39-year-old man also had splinter hemorrhages which improved with treatment [28].

Splinter hemorrhages are found in individuals at high altitude, shown nicely in a recent report of a group of adults hiking at 11,000 feet [29]. Originally described by physician and mountain climber Rennie in 1974, splinter hemorrhages were noted at 19,300 feet and were thought to be associated with trauma, exertion, and cold temperatures [30], but in Musher's group of adults, none of these conditions existed. He concluded that the principal cause of splinter hemorrhages at high altitude is due to low barometric pressure.

A number of infections have been associated with splinter hemorrhages: chronic meningococcaemia, HIV, psittacosis, rheumatic fever, septicemia, and trichinosis [1]. In psittacosis, it is the lung infection that can cause splinter hemorrhages. But recently, disseminated histoplasmosis was found in an immunocompetent traveler with prolonged fever, arthritis, and splinter hemorrhages perhaps unassociated with a concurrent lung infection [31]. In trichinosis, splinter hemorrhages are seen in up to 60% of cases of

Trichinella spiralis infections and are caused by direct damage to the vasculature caused by larval migration [32].

Splinter hemorrhages have been associated with a number of rheumatologic conditions and collagen vascular disease states, namely, acrocyanosis, antiphospholipid antibody syndrome, Behcet's disease, Reiter's syndrome, rheumatoid arthritis, Still's disease, dermatomyositis, systemic lupus erythematosus, vasculitis, periarteritis nodosa, and granulomatosis with polyangiitis [1]. It is the recognition of these nail changes in combination with highly sensitive diagnostic modalities that helps to establish an accurate diagnosis in collagen vascular disease. Tunc et al. showed that proximal nail fold erythema and telangiectasias and splinter hemorrhages in fingernails were more common in systemic lupus patients than in controls and that only splinter hemorrhages were associated with disease activity [33]. In Sjogren's syndrome, dermatomyositis and polymyositis, splinter hemorrhages, and nail fold telangiectasias were statistically more common than controls. In medicine today, criteria for the diagnosis of antiphospholipid antibody syndrome center around thrombosis and laboratory criteria. But Kriseman et al. advocate for appropriate recognition of physical signs in antiphospholipid antibody syndrome, namely, splinter hemorrhages, livedo reticularis, and ulceration which help the clinician point to the most probable diagnosis [34].

Shape

Onycholysis describes the distal separation of the nail plate from the underlying nail bed leading to the proximal extension of free air. Its association with systemic disease is overrated and is most commonly due to contact with local agents. However, inherited conditions, skin disease (e.g., psoriasis), exposure to medications, and certain systemic diseases are also associated with onycholysis. Associated systemic diseases include thyroid disease, Cronkhite-Canada syndrome, hemodialysis, diabetes, iron deficiency anemia and other hematologic conditions, rheumatologic disease, infection, and certain types of carcinoma [1]. Onycholysis has classically been associated with thyroid disease. In a recent case report in the literature associating onycholysis and Graves' disease, Malan et al. warn that any unexplained onycholysis should prompt the clinician to investigate the patient for asymptomatic hyperthyroidism [35]. Pellagra has been associated with onycholysis, and this relationship was recently re-emphasized in the literature [36]. A recent report noted onycholysis in Kawasaki disease [37], and another report associates onycholysis and subungual hemorrhages with hand, foot, and mouth disease [38]. Onycholysis is observed in pregnancy infrequently (1.9% of 312 healthy pregnant patients) and is most frequently observed at 29–42 weeks [39]. Onycholysis with some ridging, thinning, and red and white bands in association with abdominal bloating and excessive flatus was found to be the presenting signs in a case of celiac disease all resolving with treatment [40].

Nail Plate

Color

Chromonychia most commonly involves brown, white, and yellow discoloration. Chromonychia can occur in the nail plate, matrix, or nail bed. When the discoloration occurs in the nail plate, the color change is usually opaque and grows out as the nail plate grows out. Brown and white discoloration are the most common color changes observed and can be complete, partial, or linear. The pattern and color change in the nail plate can give useful clues for associated systemic disease.

Brown discoloration of the nail plate can be either linear or diffuse and can be inherited or associated with bacterial, fungal, HIV infection, endocrine conditions (e.g., Addison's disease), or medications, such as chemotherapy or minocycline [41]. Robert et al. describe melanonychia associated with chemotherapy appearing 1–2 months after the chemotherapy has begun, and it may be associated with skin and/or mucosal pigmentation [42]. Diffuse and longitudinal

melanonychia is associated with adrenal disease, Peutz-Jeghers syndrome (Fig. 9.6), and Laugier-Hunziker-Baran syndrome [1]. Patients with Addison's disease have pigmentation of the mucosa (buccal mucosa, areola, gums, and tongue), skin (nipples, areola, axilla, perineum, genitalia, and anal mucosa), and skin pressure points (elbows, knees, skinfolds, and palmar creases) and can have longitudinal melanonychia, which may be the presenting sign. Peutz-Jeghers syndrome associates pigmented macules on the oral mucosa, lips, fingers, toes, and nails with potentially malignant intestinal polyposis. Nail presentation is most commonly seen as longitudinal melanonychia of the fingernails and toenails due to melanin deposits in the nail plate. Laugier-Hunziker-Baran syndrome describes the spontaneous acquired occurrence in early to mid adult life of pigmented macules of the buccal mucosa and lips with no underlying disease process nor intestinal polyposis. Approximately half of these cases have associated nail pigmentation, most typically longitudinal melanonychia, and some patients have pigmented macules on the lateral nail fold.

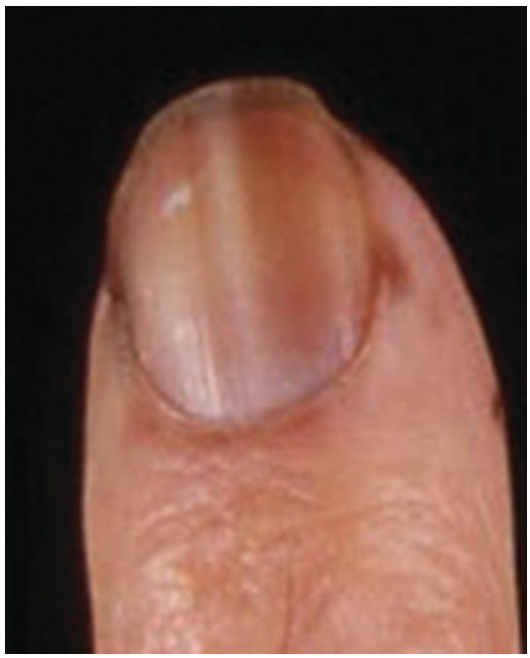

Fig. 9.6 Peutz-Jeghers syndrome

Leukonychia (white discoloration of the nail) is either true or apparent, depending on if the origin is in the matrix and consequently the plate (true) or if the origin is in the nail bed (apparent: pallor). In true leukonychia, abnormal keratinization occurs in the matrix delivering nucleated cells to the nail plate. Leukonychia can be congenital, familial, acquired, skin disease related, or associated with internal disease. Transverse leukonychia can be associated with a variety of systemic disease states, is fairly nonspecific, and has been associated with acute renal failure, heart failure, ulcerative colitis, breast cancer, infections, toxic metal exposure, and systemic lupus erythematosus [41]. It is also associated with medications such as antimetabolite chemotherapeutic agents [42]. A recent report in the pediatric literature associates transverse leukonychia with Kawasaki disease in three patients [43]. When transverse leukonychia is associated with arsenic poisoning, it is called Mees lines [44]. Arsenic can be detected in the plate, and the distance from the matrix is an indication as to when the poisoning occurred. True leukonychia can also be total (diffuse and opaque) or punctate. Another recent report associated a unilateral total true leukonychia with a unilateral multifocal neurologic motor abnormality [45]. There are other reports of neurologic-associated leukonychia, including a recent report associating acquired total and partial leukonychia with reflex sympathetic dystrophy [46]. A recent report associates a partial true leukonychia with Crohn's disease induced by selenium deficiency [47]. In a large study of 312 pregnant women, leukonychia was the most common finding in approximately one-quarter of patients examined [39]. Patient photographs indicate that these patients had punctate leukonychia.

Yellow nail syndrome is a rare condition thought to be due to functional anomalies or disturbances in pleural lymphatic drainage (Fig. 9.7). The conclusion of a 2018 study by Cousins et al. found that yellow nail syndrome is a lymphatic phenotype due to widespread upper and lower limb lymphatic insufficiency and a common mechanistic fault of poor transport found in all patients [48]. It is thought that a stress on the pleural lymphatics leads to the manifesta-

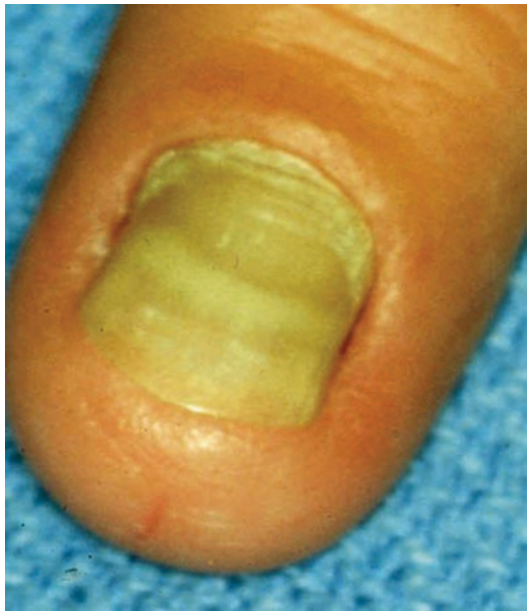

Fig. 9.7 Yellow nail syndrome

tions of this condition. Yet it also appears that the immune system may play a role. A recent report suggests that both T and B cell defects and its consequent poor response to mitogens, antigens, and infections are important in the pathogenesis of this condition [49]. Yellow nail syndrome is characterized by the triad of nail discoloration, respiratory or intrathoracic manifestations, and lymphedema. Most commonly associated with disease and malignancy of the chest and lungs, yellow nail syndrome has also been reported in association with congenital heart disease, nephrotic syndrome, rheumatoid arthritis, HIV, and a number of malignancies, including lymphoma, breast, laryngeal, and gastrointestinal tract [1]. In another recent report of the syndrome, a 39-year-old woman who underwent mitral valve replacement developed cough, dyspnea, pleural effusion, and chylothorax in association with lower extremity edema and yellow nails, all resolving with resolution of her pulmonary and chest disease [50]. Other conditions may precipitate it, like titanium from an artificial joint, dental implant [51], titanium dioxide toothpaste [52], or cardiac pacemaker [53]. In a patient with a titanium dental implant, titanium was found in nail clippings and thought to be due to the oxidative action of fluorides [54]. Patients with congenital heart disease, especially on broad-spectrum antibiotics, may be at risk of *Candida parapsilosis* onychomycosis. A 4-year-old male with a ventricular septal defect developed a yellowish discoloration subungually which showed numerous yeast elements microscopically proven to be *C. parapsilosis* [55]. Yellow nail syndrome may be congenital [56] or inherited [57]. Symptomatic relief, such as topical vitamin E and antifungal therapy, has been used with some benefit. First-line treatment should be vitamin E in a dose of 1200 IU/day which has an approximately 50% success rate [58]. Additionally, the combination of fluconazole and alpha-tocopherol stimulates linear growth and has been shown effective in a majority of treated patients [59]. A new treatment modality reported by Matsubayashi et al. showed the successful use of an anti-inflammatory macrolide antibiotic clarithromycin [60]. Intravenous immunoglobulin may help to improve the clinical manifestations of yellow nail syndrome through a potential immunomodulatory effect [61].

Shape

Clubbing is defined when the angle between the proximal nail fold and the proximal nail plate (Lovibond's angle greater than 180°) is obtuse (Fig. 9.8). It appears to be due to hypervascularity below the matrix demonstrated by high-resolution MRI with contrast [62].

Differential clubbing, clubbing in one area and normal nails in another (left vs. right or fin-

Fig. 9.8 Clubbing

gers vs. toes), allows the clinician to identify where the cardiovascular system abnormality can be found. When differential clubbing involves the toes but not the fingers, this is the hallmark of patent ductus arteriosus with reversal of shunt or aortic interruption with the ductus profusing the lower extremities [63]. Differential clubbing has also been reported in both lower extremities and the left upper limb sparing the right upper limb [64]. This occurs when the left subclavian artery originates distal to the patent ductus or when a very large-sized patent ductus causes a jet effect with selective streaming of deoxygenated blood to left subclavian artery, descending aorta, and resultant left upper extremity.

Other forms of cardiovascular disease, particularly heart disease, are also associated with clubbing. Several recent case reports of clubbing with or without cyanosis in association with an atrial septal defect with a right-to-left shunt have been reported [65, 66]. Endocarditis in a recent case in the Spanish literature reports a patient with *Listeria monocytogenes* endocarditis associated with clubbing [67]. Clubbing has been shown to resolve after removal of the offending agent. In a 63-year-old woman with infective endocarditis causing a rupture of the mitral papillary muscle, clubbing resolved after corrective cardiac surgery and antibiotics [68].

Clubbing is associated with a number of hypoxic conditions. It has been associated with pulmonary alveolar proteinosis, a condition known to occur in adults with a peak incidence in the third and fourth decade of life but recently described in children [69]. The condition is characterized by a diffuse accumulation of phospholipoprotein in the lung and associated with shortness of breath, cough, and fever. Digital clubbing is a common presentation in patients with interstitial lung disease; however, a recent study in 102 patients showed that the association is actually due to lower oxygen levels and lower pulmonary function in interstitial pulmonary disease patients [70]. Yet other studies, including one which evaluated 153 consecutive patients with interstitial lung disease, showed no association with disease severity [71]. A case report of a 49-year-old man associated clubbing with pulmonary metastases from a cutaneous melanoma [72].

Clubbing has been associated with a number of non-cardiovascular non-respiratory diseases, such as cystic fibrosis [1]. Thyroid acropachy, severe autoimmune Graves' disease, classically presents with clubbing of the fingers and toes, even in pediatric patients, in addition to pretibial myxedema [73]. Clubbing of the hands and feet and acromegaloid facial features were recently newly reported in association with a pituitary microadenoma [74]. An acute onset of unilateral painful clubbing associated with transient loss of vision was associated with a thrombosis of the left subclavian artery and polycythemia rubra vera [75]. The patient's clubbing presentation was due to the polycythemia.

Clubbing may occur in the context of a syndrome. One such syndrome, hypertrophic osteoarthropathy, is defined by six signs: clubbing of the fingers and toes, acromegalic hypertrophy of upper and lower extremities, bone pain and pathology, joint pain and swelling, peripheral neurovascular disease, and muscle weakness [1]. Periosteal reaction, polyarthralgia, arthritis, and synovitis can be associated [76]. It can occur as a primary phenomenon or, more commonly, secondary to underlying disease especially pulmonary malignancies. Hypertrophic osteoarthropathy with clubbing has recently been reported in association with pulmonary tuberculosis [77]. But it is tumors of the lung, especially non-small cell carcinoma, that have been the hallmark association with hypertrophic osteoarthropathy. Bronchogenic carcinoma is common in this paraneoplastic syndrome. However, another recent review argues that the most common primary pulmonary tumor is nasopharyngeal carcinoma and most common secondary tumor is lung metastasis [78]. A recent case report cites a 38-year-old woman who presented with clubbing of the fingers and then was found to have a solitary fibrous tumor of the pleura [79]. On examination, this patient had hypertrophic osteoarthropathy (Pierre-Marie-Bamberger syndrome) characterized by clubbing of the fingers associated with bone surface and soft tissue calcification. Treatment of the tumor in this

case improved the condition as is true in many clubbing-associated pulmonary tumors [80].

Hypertrophic osteoarthropathy is also an important presenting sign in paraneoplastic disease in gastrointestinal disease. A recent review found that the most common primary gastrointestinal tumor is esophageal carcinoma [78]. The onset of unexplained clubbing warrants the search for an underlying tumor. A case report associates clubbing with quadrant pain, fever, and vomiting found to be caused by a rare vascular hepatic tumor [81]. In a recent case, evaluation revealed a giant esophageal mesenchymal stromal tumor as the associated finding [82]. In gastrointestinal disease, the association of hypertrophic osteoarthropathy and inflammatory bowel disease is rare. There are only a few case reports in the literature including a recent one which associated Crohn's disease in a 27-year-old gentleman with hypertrophic osteoarthropathy diagnosed by x-ray radiography [83].

Koilonychia, or spoon nails, is thought to be the "opposite" of clubbing (Fig. 9.9). Increased blood flow in clubbing raises the relative position of the matrix to the nail bed raising Lovibond's angle to greater than 180°. In koilonychia, the relative position of the matrix is lower than the nail bed causing a spoon appearance in the nail plate [84]. The clinician must be aware of systemic associations in order to guide appropriate workup, treatment, and/or referral. Koilonychia may be idiopathic, familial, or acquired associated both with dermatologic conditions and systemic disease. Systemic disease associations include iron store abnormalities, anemia, Plummer-Vinson syndrome, hemochromatosis, hypothyroidism, diabetes, collagen vascular disease, and nutritional deficiencies [85]. Plummer-Vinson syndrome is rare and defined by the triad of dysphagia, esophageal webs, and iron deficiency anemia with koilonychia present in almost half of cases. It may be the presenting sign. Appropriate treatment resolves the koilonychia and the syndrome [86]. High altitude can produce koilonychia [87].

J.H.S. Beau first associated a transverse depression in multiple nails in a patient with typhoid fever in 1846 (Fig. 9.10). The distance from the matrix indicates the length of time since the insult, and the width of the depression indicates the length of time of the illness. Not a very specific sign, its presence on multiple nails more likely indicates an associated internal condition [1]. Even though J.H.S. Beau first described these transverse depressions with typhoid fever, there are many systemic diseases, infections, and medications that have been associated with Beau's lines. Antimitotic chemotherapeutic agents are a cause [42]. Multiple Beau's lines have been associated with each recurrent chemotherapy cycle

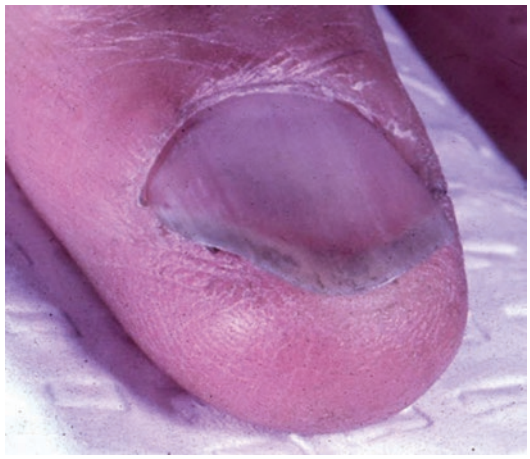

Fig. 9.9 Koilonychia

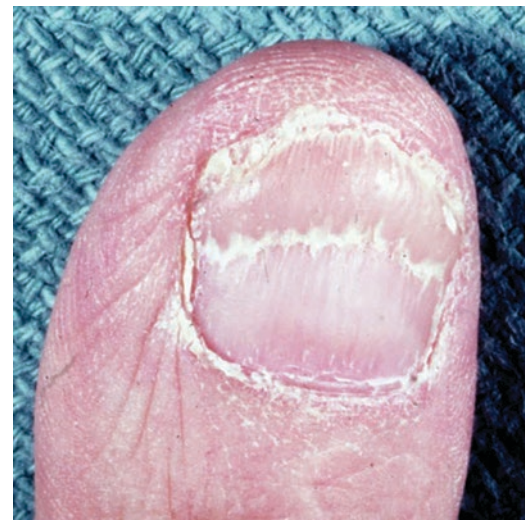

Fig. 9.10 Beau's line

[88]. A recent article by Gönül et al. described a patient with unilateral Beau's lines associated anatomically with the patient's reflex sympathetic dystrophy [89].

Beau's lines, onychomadesis (nail shedding), and retronychia (shedding at the matrix followed by embedding of the proximal plate into the undersurface of the proximal nail fold) may be variants of the same process. Onychomadesis may be a more "complete" Beau's line. In a recent article which studied both onychomadesis and Beau's lines in patients with hand, foot, and mouth disease, Chiu et al. demonstrated coxsackie A6 virus and echovirus in the nail samples of four patients hypothesizing that these virulent viruses damage the matrix and cause a transient decrease in the mitotic activity in the matrix [90].

Onychoschizia is defined as the fracturing of the distal nail plate into lamellae. It is most often associated with repeated hand washing or the use of chemicals or detergents, but onychoschizia has also been reported in systemic disorders such as anemia, polycythemia, infectious diseases, poor peripheral blood flow, and kidney transplant patients [1]. Onychoschizia represents the second most common nail change found in pregnancy, according to a study of 312 healthy pregnant women revealing an association in 9% of patients [39].

Onychorrhexis is characterized by longitudinal parallel ridging of the nail plate and can give the nail plate a rough textured appearance. It can be seen in skin disease (lichen planus, Darier's disease, and diseases associated with distal vascular lesions) and systemic disease (a common finding in rheumatoid arthritis but also seen in osteoarthritis), but it is often seen in the general population as we age [1]. The ridges gradually become more marked leading to nail plate thinning and distal splitting. It is a fairly nonspecific sign. In a case-controlled study of 400 Egyptian patients, onychorrhexis was seen in just under half (45.5%) of those over 60 years of age [91]. Classically, onychorrhexis is associated with rheumatoid arthritis. A recent case report associates sarcoidosis of the lungs and nose with pathologic confirmation of sarcoidosis of the nail [92]. Clinical presentation of the nail changes revealed onychorrhexis but also a progressive longitudinal erythronychia in the toenails which improved with intralesional corticosteroid treatment.

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Brittle Nails

10

Solomon Geizhals and Shari R. Lipner

Abbreviations

FDA	Food and Drug Administration
HPCH	Hydroxypropyl chitosan
TOWL	Transonychial water loss

Anatomy of the Nail

The nail plate is a fully keratinized structure that is 0.5–1 mm thick and is produced by the germinative epithelium of the nail matrix. Under normal conditions, the mean growth rate of a fingernail is 3 mm/month and that of a toenail is 1 mm/month. The matrix consists of an epithelium that keratinizes without the formation of a granular layer and is made up of three distinct layers:

- The dorsal nail plate (0.08–0.1 mm thick) is produced by the proximal portion of the nail matrix and gives the nail plate its characteristic hardness and smoothness.
- The intermediate nail plate (0.3–0.5 mm thick) is produced by the distal matrix and gives the nail flexibility.
- The ventral nail plate (0.06–0.08 mm thick) is produced by the nail bed and is necessary for the adhesion to the nail plate [1].

Nail plate keratinocytes consist of 80–90% hard, hair-type keratin filaments and 10–20% soft, epithelial-type keratin filaments that are orientated in multiple directions. In the α-keratin filament predominant middle layer, the filaments are oriented perpendicularly to the growth axis. The dorsal and ventral layers are composed of epidermis-type keratin filaments which are oriented parallel and perpendicular to the growth axis [2].

Sulfur makes up approximately 10% and calcium makes up 0.2% of the nail plate by weight, respectively. The remaining principal minerals include magnesium, calcium, iron, zinc, sodium, and copper [3]. Healthy nails contain up to 5% lipids filling certain ampullar dilations of the dorsal plate and intercellular spaces in the ventral plate [1]. These lipids, particularly acylceramides, coupled with the disulfide bonds of cystine and desmosomes, are considered the main contributors to nail hardness and are referred to as the intercellular "cement" [4, 5]. They work in sync via cross-linking α-helix keratin fibers together between the corneocytes, all held together by hydrophobic interactions, forming a water-impermeable layer [6].

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Risk Factors and Pathogenesis

The factors that are critical to the integrity of the nail plate include the following:

1. The intracellular skeleton structure of keratin fibrils
2. Keratin-associated proteins that form the matrix between keratin filaments
3. Lipid bilayers
4. Desmosomes

Epithelial growth and keratinization occur in both the nail matrix and nail bed and are responsible for creating a normal nail plate. Environmental factors, both chemical and mechanical, may damage intercellular adhesion of the nail plate corneocytes, causing lamellar peeling known as onychoschizia (Fig. 10.1). The longitudinal ridges and splits, known as onychorrhexis (Fig. 10.2), are caused by fluctuations in nail plate production by the matrix. Nail matrix vascularization and oxygenation are crucial for normal keratinization [7]. The primary pathology of brittle nails is believed to be secondary to nail plate hydration and/or nail matrix or corneocyte abnormalities. Family history and genetic predisposition contribute to the pathogenesis [8, 9].

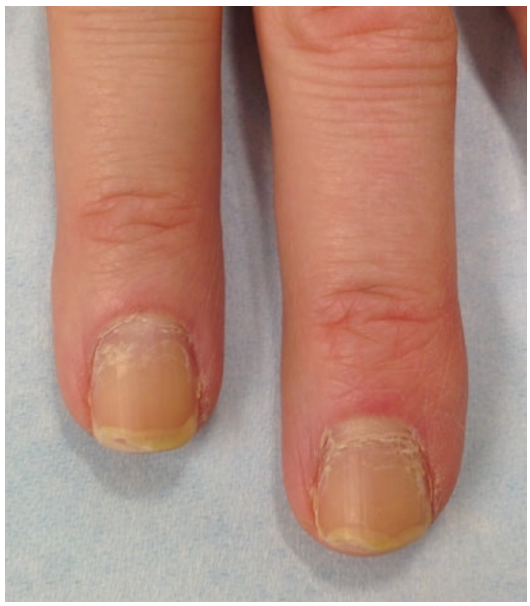

Fig. 10.1 Onychoschizia: lamellar splitting of the free edge of the nail plate generally attributed to intercellular fractures of nail plate corneocytes

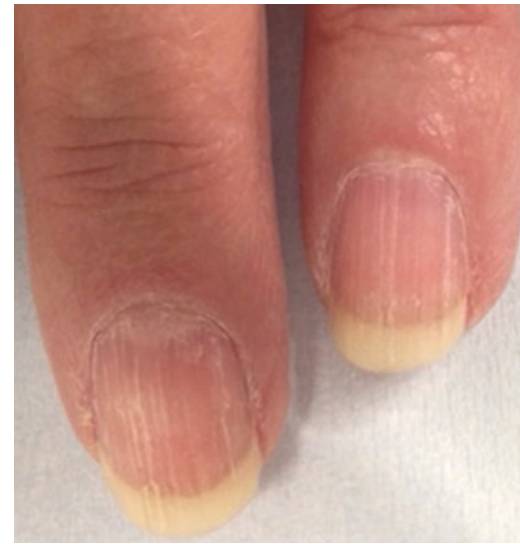

Fig. 10.2 Onychorrhexis: fissuring of the longitudinal nail plate generally attributed to nail matrix dysfunction

Nail plate hydration is thought to be a significant factor in the pathogenesis of brittle nails [10]. It was generally accepted that baseline nail water content is approximately 16–18%, and the nail becomes brittle when it becomes less than 16% and soft when greater than 25% [11]. Transonychial water loss (TOWL), defined as water escape through the nail plate, is relatively high compared to the stratum corneum, although this has been challenged [12–14]. It is difficult to replace water lost from the nail plate because extensive soaking paradoxically results in enhanced water loss, not rehydration [15].

Utilizing a "nail flexometer" on cadaver nails, Finlay et al. noted the increased flexibility of the nail plate after immersion in water, implying increased moisture content is a significant factor for flexibility. Moreover, they noted that the nail maintained its enhanced flexibility after the application of mineral oil or phospholipids on the nail, implying that one can trap the increased moisture with a hydrophobic seal [16]. Raman spectroscopic studies on the nail plate confirmed that mechanical properties are directly related to nail plate water content [17].

The importance of nail plate water content in the pathology of brittle nails has been challenged. In one study (n = 102), the authors found that there was no statistically significant difference in water content between patients with brittle nails (11.9%) and healthy patients (12.5%). Moreover, participants of the study who used hand moisturizers frequently had 6.57 greater odds to suffer from brittle nails (95% CI 1.35, 32.10) than those with healthy nails [8]. Nevertheless, while water content in it of itself may not be a risk factor for brittle nails, excessive hydration and desiccation likely disrupt intercellular lipid lamellae [18, 19]. Wetting and drying cycles of the nail plate can result in contraction and expansion of the nail, damaging corneocyte adhesion, specifically manifesting itself as in onychoschizia, in women, in thumb-sucking infants, and during the changing seasons [20–24]. This is supported by the finding of decreased sulfur content in 77.3% of patients (n = 55) with dystrophic nails, implying a paucity of disulfide bridges weakening the corneocyte-based infrastructure of the nail plate [25].

Occupational exposure to chemicals, thioglycolates, cement, solvents, alkalis, acids, anilines, salt, and sugar solutions can all dissolve intercellular lipids, causing fractures between corneocytes leading to brittle nails [26]. Although nail lacquer alone is not deemed a risk factor in and of itself, excessive use of polish removers, hardeners especially those containing formaldehyde, cuticle removers; special nail procedures such as nail wrapping, sculpturing, premixed acrylics, and gel polish; and the improper use of manicure tools can all create intercellular fissures in the nail plate [27–30]. Occupational contact with a variety of solutions and solvents can lead to progressive dehydration of the nail plate and is found in shoemakers, carpenters, and even tea pickers [31, 32].

The prevalence of brittle nails in these occupations may also be attributed to repetitive bouts of microtrauma, which may account for the increased prevalence found in chemical and medical personnel, photographers, painters, and musicians [1, 33]. Normal activities of daily living may also contribute to traumatic brittle nails such as typing, dialing, improper nail clipping, onychotillomania, and onychophagia [1, 34, 35]. Although the increased prevalence of brittle nails in women has been attributed to a heightened cosmetic consciousnesses, other factors are likely involved including household chores (either due to increased water exposure or microtrauma) [1], a constitutional fragility relative to males [23] (possibly due to their thinner nail matrix [36]), slower nail growth rates relative to men, [37] decreased lipid content in aging women [38], or possibly to postmenopausal changes [39].

Fungal infections can traumatize the nail plate, fracturing both intracellular and intercellular via fungal proteolytic activity, crumbling the nail plate, and increasing the susceptibility of idiopathic nail brittleness [21]. Although other dermatological conditions may cause brittleness, they often present in a variety of ways other than onychorrhexis and onychoschizia. These include the thinning, longitudinal ridging, and distal splitting of lichen planus [40] and lichen striatus; the longitudinal streak with distal splitting at the nail's free edge of Darier's disease [1]; the lamellar exfoliation of eczema; the rough, sandpapered nails of trachyonychia [41]; the grid-like and superficial pitting of alopecia areata [42]; and the irregular and deep pits of nail psoriasis [43]. The overlapping features of these pathologies led to the hypothesis that chronic inflammation contributes to brittleness [44].

Secondary nail brittleness can be caused by a variety of systemic diseases, nutritional deficiencies, and drug intake. Systemic diseases generally cause brittle nails via effects on nail keratinization. Arteriopathy, vasculopathy, and neuropathy may lead to poor perfusion of the nail matrix, producing a weak nail plate. This can be seen in diabetes, Raynaud's phenomenon, polycythemia vera [45], and systemic sclerosis [46]. Thyroid disease, more commonly in hypo- than hyperthyroid, can cause both soft and brittle nails but is often reversible following successful therapy [47]. Increased nail fragility, onycholysis, and longitudinal ridging can all occur in Sézary syndrome [48], amyloidosis [49], graft-versus-host disease, and rheumatoid arthritis [50]. Syphilis [51] and leprosy [52] have been associated with nail thinning, fragility, and brittleness. Liver disease, such as cirrhosis, HBV,

and HCV, can all cause a variety of nail changes including brittle nails [53]. Chronic infectious diseases including pulmonary tuberculosis, empyema, bronchiectasis, and sarcoidosis can impair nail formation causing brittleness [9]. A case of recurrent malignant glucagonoma was diagnosed due to brittle nails and dyspareunia [54]. Nail pathologies, including trachyonychia [55], melanoma, squamous cell carcinoma, warts, onychopapillomas, and pyogenic granulomas, may present with longitudinal abnormalities that can present as fragile nails [56].

Nutritional deficiencies may result to nail fragility and thinning. Vitamin A, vitamin B6, vitamin B12, vitamin C, vitamin D, and vitamin H (biotin) are all integral to nail growth and improve nail strength while reducing moisture loss [1]. Although the pathogenesis is unknown,the concentration of these elements in brittle nails is not significantly different from the concentration in normal nails; however, a deficiency of iron, zinc, calcium, and magnesium can all lead to brittle nails and onycholysis [57, 58]. As such, a decreased dietary water or food intake, a common phenomenon among and those suffering from anorexia nervosa [59], bulimia [60], and the elderly [3], can all lead to an increased prevalence of brittle nails.

Systemic drugs such as chemotherapeutics, antiretrovirals, and retinoids can all contribute to the pathology of brittle nails [61–63]. Patients treated with MEKIs, EGFRIs, mTOR inhibitors, and ibrutinib have all been noted to cause onychodystrophy including brittle nails and possibly a slower nail growth rate [64]. With antiretrovirals and retinoids, most notably etretinate [65] and oral isotretinoin [66], it is common for the nail plate to break easily and give rise to tiny spicules that penetrate the periungual furrows causing the formation of pseudo-pyogenic granulomas [1]. Abnormal keratinization may result from previous irradiation or arsenic use, leading to brittle nails as well [3].

Pregnancy can also induce nail changes including transverse grooving, brittleness, and softening. These changes may occur as early as the sixth week of pregnancy. These changes can be attributed to rapid nail growth causing delayed keratin maturation due to increased estrogen [67]. On the other hand, the slow linear growth of nails has also been implicated by some as a cause for the greater prevalence of brittle nails in the elderly, whose nails grow much more slowly than in the young [68], and in women in general [37], leaving the status of nail growth as an impetus for brittleness unclear and may merit further investigation.

Epidemiology

In 1940, Silver et al., in a comprehensive cross-sectional study of brittle nails, showed that 18.4% (n = 994) of the general population were affected by brittle nails. Similar prevalence of 19.6% was later confirmed by Lubach et al. in 1986 (n = 1584) [27, 31]. Silver and Lubach both noted that women were affected in a 2:1 ratio compared to men, with similar findings replicated in a cross-sectional study of patients wearing daily occlusive gloves [27, 31, 69]. Gequelim et al. observed that 57% of female dermatological patients suffered from brittle nails but commented that the higher percentage may be due to selection bias, as the patient population was limited to dermatological patients, as opposed to the prior studies which included a more generalized populace. Additionally, the methodology used by Gequelim employed the van de Kerkhof criteria for brittle nails, while the older studies utilized subjective analysis [7, 34].

Those greater than 60 years old have a greater prevalence of brittle nails [70], with one study (n = 200) finding that 67.5% of elderly Egyptians were affected compared to 5% under the age of 60 ($p < 0.001$) [71]. Lubach found this discrepancy more pronounced in males; only 12% of younger males were affected compared to 31% of elderly males, while 29% of younger females reported brittle nails compared to 36% of elderly females [12]. Women between the ages of 40–60 most frequently suffer from brittle nails, with one study finding that it affected up to 30% of women over 50 years old [1]. Lubach noted that 35% of women aged 31–40 (n = 113) also suffered from brittle nails [31]. Although not statistically sig-

nificant, two studies found an increased prevalence of brittle nails, specifically onychoschizia, in infants [20, 72].

Brittle nails are more common in fingernails compared to toenails, with one study having 94% and 6% affected, respectively [34]. Increased frequency of involvement of the first three digits of the dominant hand has been reported with Gequelim reproducing these findings albeit without differentiating between dominant and nondominant hands [34, 73]. However, Weistenhöfer et al. only found increased prevalence in the first digit [69]. Increased prevalence of brittleness in the hands relative to feet, as well as to the first three digits, can be attributed to increased exposure to the environment and trauma of those areas, specifically in those presenting with onychoschizia [22, 74]. In contrast, onychorrhexis is a phenomenon largely associated with aging [1].

One survey-based study found that patients who were black/mixed race, were atopic, or had a depressed mood had an increased perception of nail fragility even though there was no evidence of such according to clinical definitions [34]. Patients tend to perceive brittle nails differently from physicians, often skewing survey data and potentially underreporting true prevalence; hence, physical examination is crucial for data records [8].

History and Clinical Presentation

Brittle nails are generally presumed to be a cosmetic problem, but when dystrophy is severe, functional capabilities can be affected as well. Patients generally complain of soft, nongrowing, dry, weak, and easily breakable nails [9]. Although some have proposed as many as six clinical findings of brittle nails [65], much of the literature tends to emphasize two pathologic variants [8]:

1. Onychorrhexis—superficial, parallel longitudinal ridging in the nail surface that can often result in splitting on the distal free edge (see Fig. 10.2). It may also present with multiple crenulated splits, characterized by triangular fragments at the free edge that are easily torn off [7]. Onychorrhexis has been reported as the strongest association with nail fragility perception [34].
2. Onychoschizia—horizontal layering frequently seen in the form of lamellar splitting of the distal free edge of the nail plate (see Fig. 10.1). Onychoschizia may also include breaking of the lateral edges, causing transverse splitting which can lead to loosening of at least one-third of the distal nail plate [7].

Kerkhof et al. and Sherber et al. each proposed their own semiquantitative grading system that allows for the calculation of an average score reflecting the level of severity, thereby allowing an objective means of following progression because in many patients, brittle nail changes are mostly subjective [7, 75]. Although primarily a clinical diagnosis, dermoscopy is a useful tool in diagnosing brittle nails. It can assist in identifying longitudinal ridges, superficial pits, and lamellar splitting especially in early stages of mild disease [76].

Treatment and Management

Therapeutic approaches to brittle nails should first be targeted to eliminating eliciting factors followed by general measures and more specific therapies. If possible, it is important to determine and treat brittle nail etiology, such as nutritional deficiency and dermatological, infectious, or a systemic condition, as that may improve or even cure the nail brittleness [9]. Secondary nail brittleness often damages the nail matrix and tends to involve the entire nail plate. However, most patients with brittle nails have an idiopathic nail fragility, usually caused by internal or external damage to the intercellular keratinocytes causing onychorrhexis and onychoschizia. Physicians should always inquire if both the fingernails and toenails are brittle. In majority of the cases, only the fingernails are affected. It is therefore integral to stress that external factors play a pivotal role [56]. As mentioned above, onychorrhexis is more

associated with older age and onychoschizia with water exposure; however, this is not absolute.

Some general measures focus on increasing the water content of the nail, especially in onychoschizia, as well as minimizing trauma (Table 10.1). Frequent hydration by soaking in lukewarm water for 15 minutes daily is helpful [77]. Gloves are recommended to reduce prolonged water immersion and avoidance of irritants, although extensive use of occlusive gloves can also lead to softened and brittle nails [69]. Avoidance of hand sanitizers that contain triclosan is preferred as triclosan eliminates water from the nail plate to a greater extent than traditional washing [56]. Patients are also advised to limit the use of nail polish removers (especially those that are acetone based), nail prostheses, and gel and acrylic nails. Identifying and subsequently minimizing microtrauma that includes any rubbing, friction, and drying are recommended. This is especially common during improper and repetitive manipulations in nail salons where multiple risk factors are commonplace. Patients should remain vigilant in avoiding cuticle tampering and the use of sharp instruments under the nail plate surface for cleaning, as well as having nails filed in only one direction [56]. The nails should be kept short and squared to minimize trauma, and after any soaking, nails can be rehydrated with topical moisturizers [1].

Many supplements including a multitude of vitamins, oligo-elements, and amino acids claim to improve brittle nails. These include biotin (vitamin H), application of essential fatty acids, ingestion of vitamin C, vitamin D, primrose oil, ascorbic acid, pyridoxine, amino acids, silicon [78] and gelatin [79], L-methionine, keratin, pantothenic acid, salt, millet, yeast, chromium, and rhodanates [80, 81]. Topical gelatin and botanical extracts are promoted to strengthen brittle nails, but no clear evidence exists [76]. Iron supplementation may be considered when systemic ferritin levels are below 10 ng/mL [1]. Oral γ-linolenic acid (GLA)-rich borage oil has been promoted for treating brittle nails based on anecdotal evidence that prostaglandin E1 helps improves the strength of keratin-dependent tissues [21]. One recent study (n = 25) found that after ingestion of 2.5 g of a specific bioactive collagen peptides (BCP, VERISOL®), brittle nails improved by 88% via clinical assessment, as well as causing a notable decrease in frequency of broken nails. It was hypothesized that the improvement was due to increased protein intake and the stimulatory effects of collagen peptides on epidermal and dermal metabolism [82]. As an open, non-controlled trial, certain inherent biases should not be discounted, including potential behavioral changes of some of the patients.

Marked biotin deficiency is associated with poor nail quality [80]. After it was discovered that biotin improved the hardness of pig claws and horse hoofs [83], there was interest in this vitamin for treating human brittle nails, which are also keratin based. Biotin, an important regulator of lipid synthesis, is believed to be beneficial by improving the quality of intercellular lipids [21]. Subsequent trials and studies were done which showed some improvement in firmness and hardness of the nail after taking varying dosages of oral biotin [84, 85]; however, the parameters of these studies were not ideal, including small sample size and unknown baseline biotin levels. Likely due to its low cost, over-the-counter availability, and glamorization in the media, biotin has become an overwhelmingly popular recommendation from physicians to improve skin, hair, and nails [86]. However, a recent warning issued by the Food and Drug Administration (FDA) stated that ingestion of biotin can significantly interfere with laboratory tests [87], including some

Table 10.1 Recommendations for treatment of brittle nails: general measures

General measures
Soaking nails in lukewarm water for 15 min daily
Wearing gloves (avoiding prolonged water and irritant exposure)—ideally cotton gloves worn inside rubber gloves
Avoidance of triclosan-based hand sanitizers
Limit nail cosmetics (nail paint removers, prostheses, gels, and acrylics)
Minimizing nail trauma (overzealous manicurists, nails should be kept short and squared, avoiding shattering/chipping of free edge via nail filing in only one direction and using sharp nail cutters)
Moisturizing the proximal nail plate and cuticle

immunoassays, troponins, and thyroid function tests. As the evidence supporting biotin is weak and may have adverse health effects [80], the risks and benefit of treatment with biotin for nail diseases should be carefully weighed for each nail patient [88, 89].

Stern et al. reported that those that applied hand emollients frequently had a high prevalence of brittle nails [8]; nevertheless, moisturizing the periungual area has been recommended, especially with emollients containing phospholipids [16]. Since TOWL is high during water immersion, nail water content may be increased with a hydrophobic seal [90] or moisturizer. Urea (5–20%) and alpha hydroxy acid (5–10%)-based moisturizers are both efficacious options in increasing water-holding capacity of the nail. The hydration is only temporary, however requiring two applications per day, but too frequent applications can wear away the nail plate. Moisturizers rich in glycerin and petrolatum should be applied more frequently than twice per day [15]. Moisturizing while occluding with cotton gloves or saran wrap is helpful, preferably at bedtime for at least three months, to help increase emollient penetration [91].

Cosmetic treatments may camouflage nail abnormalities but do not address the underlying issue and may cause adverse reactions. These include nail polishes, hardeners, strengthening agents, builders, wraps, and artificial nails. Lacquers or polishes typically enhance nail hardness and prevent contact of detergents with the nail. Nail polish slows down water vapor loss from 1.4 to about 0.6 mg/cm^2/h, stabilizing water content, although this is variable depending on the type of polish used [92, 93]. However, the continuous use of nail polish can damage the superficial layers of the nail plate, resulting in fine and scaling white spots on the nail plate. Hardeners are theoretically ideal for soft nails; however, they contain formaldehydes. Formaldehydes strengthen the nail plate by creating more keratin cross-links but are also drying. Strengtheners are recommended for fully developed nails that are prone to splitting, while builders for thin, poorly formed nails. Gel nails, wraps, and artificial nails are mainly meant to afford protection and camouflage [91, 94]. Although these cosmetics have some utility, use of nail polish remover causes increased nail dehydration and increased risk of brittleness [15]. Some precautions may be instituted with gel nails to avoid these adverse effects, including only applying one layer of gel and decreasing acetone nail remover exposure if feasible [94].

Prescription medications are also utilized to treat brittle nails, with most based on the principle of restoring the affected nail and maintaining a normal degree of hydration (Table 10.2). Since it was believed that chronic inflammation plays a role in brittle nails, a randomized controlled study (n = 24) was performed utilizing topical cyclosporine to treat this condition. There was no statistically significant difference between cyclosporine with emulsion and emulsion alone ($p < 0.05$ each) when comparing each with untreated brittle nails [95]. In an open-label study (n = 20), patients with brittle nails applied tazarotene 0.1% cream twice daily for 24 weeks. A 89.5% subjective improvement was endorsed by the patients in surveys, and a semiquantitative grading system showed a 73.7% overall improvement in brittleness [75]. Genadur® is a hydrosoluble lacquer formulated from *Equisetum arvense*, or horsetail, extract, methylsulfonylmethane and hydroxypropyl chitosan (HPCH) [96]. When applied to the nails, it forms a highly elastic, smooth, and almost invisible film that adheres to the nail structures, protecting them against physical injuries [4]. In a comparative study (n = 34) between HPCH-based lacquer and another lacquer of a similar composite-lacking HPCH, there was a 74% overall clinical improvement and an 80% improvement in cases of severe onychoschizia noted by the investigators [97]. Another available topical is a lacquer made of 16% polyurea urethane, marketed as Nuvail™, that, when applied to the nails, adheres tightly to the surface providing a protective layer that prevents direct injury, provides mechanical support, and possibly augments the formation of new, healthy nail from the nail matrix by improving cellular migration [98].

Table 10.2 Medical treatment of brittle nails and supporting evidence

Topical medication	Supporting study	Proposed mechanism of action	Treatment regimen
Topical cyclosporine emulsion 0.05%	Mackay-Wiggan et al. [95] 36-week, single-center, double-blind, randomized study *n* = 24 90% improvement based on patient surveys	Anti-inflammatory action coupled with moisturizing emulsion	Twice daily for 24 weeks
Tazarotene cream 0.1%	Sherber et al. [75] 36-week, open-label, single-center, investigator-initiated trial *n* = 20 73.7% clinical improvement	Receptor-selective synthetic retinoid Normalizes epidermal differentiation and reduces inflammation	Twice daily for 24 weeks
Hydroxypropyl chitosan-based lacquer	Sparavigna et al. [97] 4-week, open label, randomized hand selection to either HPCH-based or non-HPCH-based, single-center trial *n* = 34 Clinical improvement in 80% in those with severe onychoschizia	Combination of horsetail extract, methylsulfonylmethane, and hydroxypropyl chitosan Strengthen the nail, supports nail growth, and improves hydration	Once daily application at bedtime
16% polyurea-urethane	None to date Anecdotal evidence	Adheres to the surface providing a protective layer and mechanical support Enhances cellular migration	Once daily application at bedtime

Conclusion

Brittle nails are a common, yet complex problem that is distressing for patients and physicians alike. Currently, there is a lack of consensus regarding multiple aspects of brittle nails including degree of physical manifestations, pathophysiology, and treatment regimens. If an underlying cause cannot be found, then the brittle nails is most likely multifactorial, caused by a combination of intrinsic nail fragility and environmental exposure to damaging substances. General preventative measures including minimizing nail trauma, avoiding prolonged water exposure, limiting nail cosmetics, and moisturizing should always be advised, and tazarotene cream, HPCH-based lacquer, or 16% polyurea-urethane can also be helpful.

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11 The Nail Involvement in Leprosy and Sporotrichosis

Robertha Carvalho de Nakamura

Tropical diseases refer to infectious diseases that thrive in hot, humid conditions that occur solely, or principally, in the tropics. Most often, they become chronic infectious diseases.

These can be grouped, based on the microorganism, into bacterial, fungal, and viral. Among them are leprosy and sporotrichosis. Leprosy is a destructive bacterial disease that often affects the hands, fingers, and nail unit. Sporotrichosis are caused by dimorphic fungi with saprobiotic life in nature. As it is not common to affect the nail unit, a high index of suspicion is required for the early diagnosis of tropical diseases [1].

They may occur in the nail unit on primary form or more rarely in the disseminated form. Each type of bacterial or fungal infection has a "classic" presentation [1, 2].

They are referred to as "neglected diseases" for they arouse little interest from the pharmaceutical industry and health agencies. Thus, they do not provide the sufficient means to study and management. For many, the use of the concept of emerging and reemerging diseases is more appropriate [1].

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Leprosy

Leprosy is an infectious disease, granulomatous, and curable caused by *Mycobacterium leprae*, an obligate intracellular pathogen. It infects Schwann cells in the nerve and macrophages in the skin. It evolves chronically and may have periods of exacerbation called reactions [3].

The disease is practically eliminated in developed countries. However, it is a public health problem in poor and developing countries such as Brazil and India, which alone account for over 80% of new cases in the world [3].

According to the World Health Organization, there has been a reduction in the number of new leprosy cases. This occurred after the introduction of the multidrug therapy scheme in the early 1980s. The epidemiological profile shows no gender preference, and the incidence is higher among young adults (25–40 years). The manifestations, clinical, bacteriologic, and histological, are affected by the patient's immunological status, which also determines the prognosis [3, 4].

The lack of knowledge and lack of primary health care make the disease the leading cause of nontraumatic disability with a high morbidity rate. It is estimated that around 30% of leprosy patients develop some form of disability [1, 3].

Some studies have shown a similar prevalence of nail changes in leprosy in both multibacillary (MB) and paucibacillary (BP) patients. Others state that nail changes are more frequent in MB

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patients. This is limited information. Further studies are needed to obtain data representative of the prevalence of nail changes in leprosy [4–7].

The alterations of leprosy can be prolonged and often irreversible. Patients with severe and lasting peripheral nerve involvement develop hand and foot deformities that compromise the nail unit. Onychodystrophies in leprosy patients are common. Common injuries are foot drop, clawed hands, and ulcers on feet or hands [3] (Figs. 11.1, 11.2, and 11.3).

Factors Associated and Nail Changes in Leprosy

The factors that trigger nail changes are numerous and include neuropathy, repeated trauma, bone changes, vascular insufficiency, infections, lepra reactions, and the drugs used to manage the disease (Table 11.1) [3–5, 7].

The main factor of onychodystrophy in leprosy is peripheral *neuropathy*. As a result of neurological damage, there can be a loss of sen-

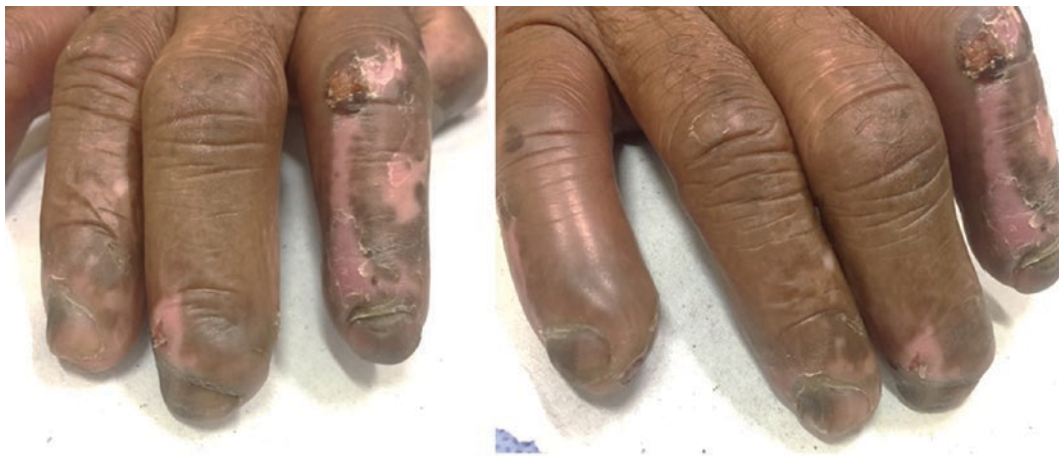

Fig. 11.1 Clawed hands and ulcer on hands

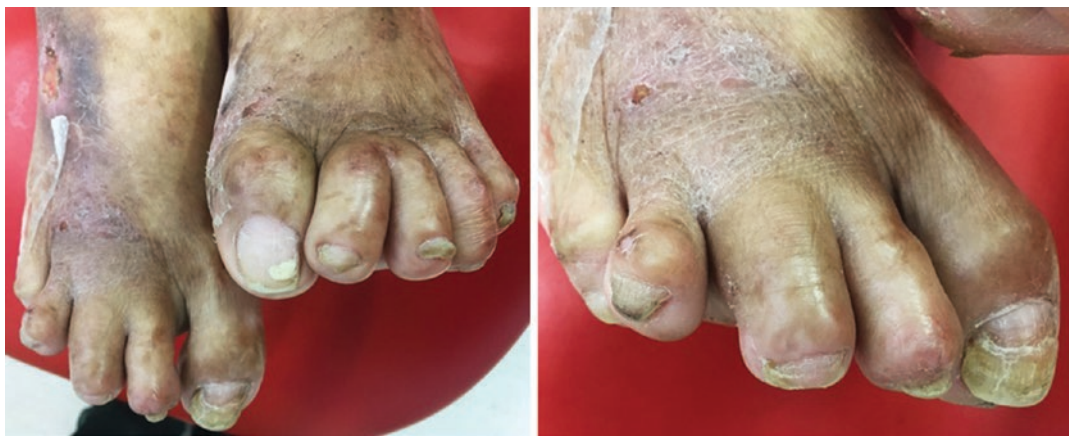

Fig. 11.2 Foot drop and ulcers on feet

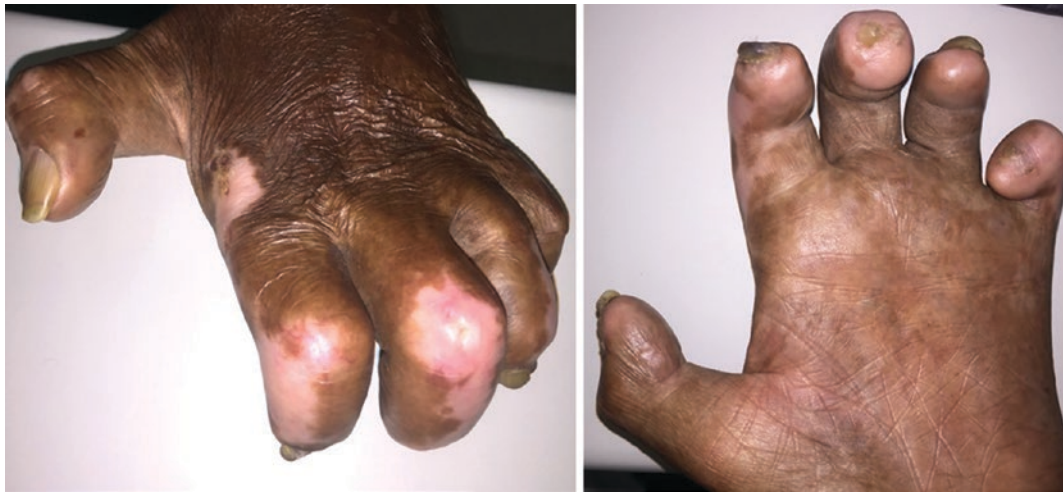

Fig. 11.3 Clawed hands and osteolysis of the last phalanges with the loss of the tips of the fingers

Table 11.1 Correlation between factors associated and nail changes in leprosy

Factors associated of leprosy	Nail changes
Neuropathy	Onycholysis, onychauxis, onychogryphosis, pterygium unguis, melanonychia, and nail loss
Trauma	Subungual hematoma, onycholysis, Beau's lines, longitudinal ridging, splitting, pterygium unguis dorsal, and longitudinal melanonychia
Acro-osteolysis	Brachyonychia, racket nail, and anonychia
Vasculopathy	Flag sign, pterygium unguis ventral, and pallor of nail
Infection	Onychomycosis and paronychia
Type 2 lepra reaction	Pterygium unguis, Beau's grooves, and nail loss
Drugs	Beau's groove, subungual hyperkeratosis, onycholysis, melanonychia, longitudinal striae, pitting, macrolunula, Terry's nails, leukonychia, and hapalonychia
Multifactorial	Melanonychia, pitting nail, pseudomacrolunula, true leukonychia, hapalonychia, pallor of nail, Terry's nails, and flag sign

sitivity, anesthesia, and a deformity of the fingers and toes. Onychodystrophies are highly varied and nonspecific and mostly occur as a result of nerve involvement [5, 8–10].

The misuse and disuse of anesthetic and deformed hands and feet result in repeated mechanical and thermal trauma, developing ungual alterations like onycholysis, onychauxis, onychogryphosis, pterygium unguis dorsal after trauma or ventral after vasculopathy, and melanonychia. Other changes include infection and osteolysis of the last phalanges with the loss of the tips of the digits and therefore their nails [3, 5, 8–10].

Onychodystrophies due to *acro-osteolysis* that occurs in the advanced stages of the disease are present as with brachyonychia, racquet nails, or even anonychia [11].

Complete shedding of the nails, brachytelephalangia, and rudimentary nails with loss of terminal phalanges were the changes found exclusively in MB patients. This is consistent with the hypothesis of Baran and Juhlin which states that development of a normal nail is dependent on the underlying bone. Anonychia or micronychia may result when the underlying bone is either hypoplastic or completely absent. In leprosy, it is possible that nails may be affected secondary to resorption of distal phalanges [5, 12].

Trauma is more common in MB patients probably because anesthetic but functional limbs are more frequently traumatized. In these patients, in the early and most active stages of the disease, neurological impairment is not intense [3, 5, 11].

Nail changes due to trauma are referred like subungual hematoma, onycholysis, Beau's lines, longitudinal ridging, splitting, and pterygium. Longitudinal melanonychia is a common change observed in PB and MB cases. These bands arise due to stimulation of melanocytes in the nail matrix following repeated trauma [3, 5, 13].

There may be *infections* due to *Pseudomonas aeruginosa* causing green nails and staphylococci causing paronychia. In case of osteomyelitis, this can contribute to acro-osteolysis. Brand confirmed with follow-up radiographs over a period of 5 years that approximately 95% of resorption resulted from open wounds developing a secondary infection [8].

Candidal onychomycosis is rarely seen in leprosy. This is justified by the existence of cutaneous xerosis in these patients who modify the environment, making it unfavorable to the growth of some fungi like *Candida albicans* [6, 11].

The nail changes due to peripheral *vascular deficiency* occur mainly in patients with chronic involvement of the skin and subcutaneous tissue at the extremities. Local fibrosis and lymphatic edema accompany the neurovascular plexus. Common changes are flag sign, pterygium, and pallor of nails [3, 9].

The specific impairment in lepromatous leprosy affects dermal vessels, subcutaneous tissue vessels, and eventually larger-caliber peripheral venous vessels. Regarding arterial involvement, it is restricted to the small arteries of the deep dermal plexus. This impairment is restricted to the most active phases of the disease [3].

The type 2 *lepra reaction* may appear before the diagnosis of leprosy during treatment or at the end of treatment. The vasculitis occurs due to thromboangiitis obliterans during this reaction (erythema nodosum leprosum reaction) with the consequent production of immune complex [4, 9, 11].

Usually, it presents as erythematous subcutaneous nodules, neuronal damage, and multiorgan involvement. In this process, there is iridocyclitis and orchitis, and systemic manifestations such as fever, arthritis, lymphadenitis, neuritis, or nephritis may appear. At the nail can occur pterygium, Beau's grooves, resorption of distal phalanges, and distal tissue loss, sometimes including nails [9, 14, 15].

Drugs used in leprosy therapy (dapsone and clofazimine) can cause nail changes due to their adverse effects. They are Beau's grooves, melanonychia, onycholysis, longitudinal striae, pitting, macrolunula, Terry's nails, leukonychia, and hapalonychia [11, 16].

Subungual hyperkeratosis was another change. Though the exact explanation is not known, this has been speculated to be the adverse effect of clofazimine therapy given in anti-inflammatory doses. Pallor of the nails noted in PB and MB patients, though not being specific for the disease, can probably be attributed to anemia due to the anti-leprosy drugs, notably dapsone, and partly due to disease itself and also vascular deficit secondary to vessels involvement [4, 5, 16] (Figs. 11.4, 11.5, 11.6, 11.7, 11.8, 11.9, 11.10, 11.11, 11.12, 11.13, and 11.14).

Diagnosis and Management

Nail changes are common in leprosy, but they are not specific. In the diagnosis of nail changes in leprosy, it is necessary to understand the regional characteristics of nail involvement. At lepromatous leprosy patients, nail changes usually occur

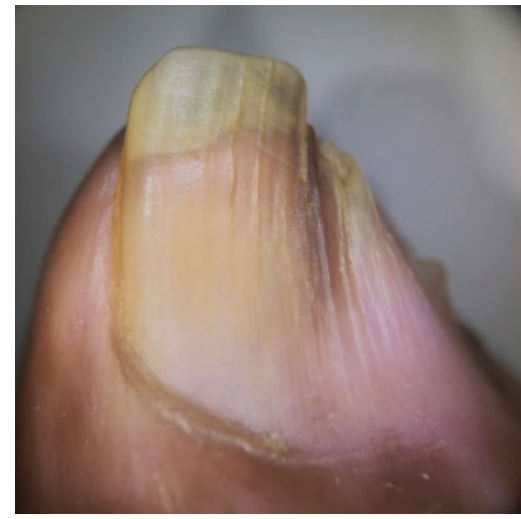

Fig. 11.4 Onychorrhexis and melanonychia, change of the tips of the fingers, and therefore of the nail form

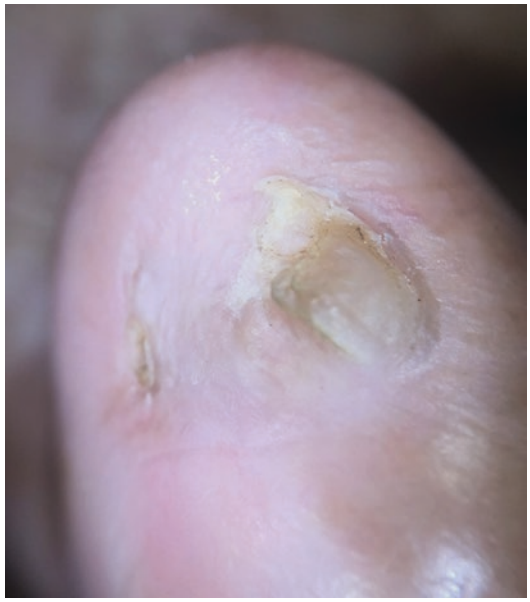

Fig. 11.5 Micronychia and partial nail plate loss

Fig. 11.6 Resorption of distal phalanges, change of the tips of the fingers, micronychia, and alteration of the longitudinal curvature of the nail plate

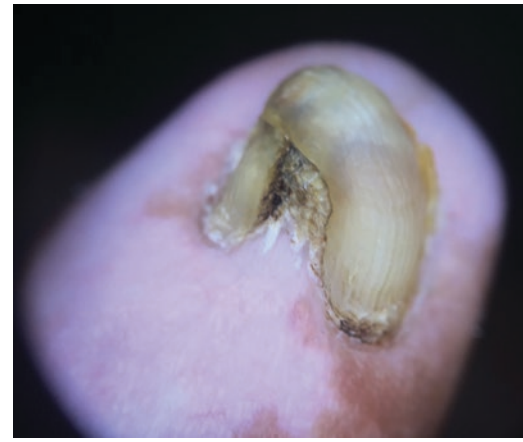

Fig. 11.7 Pterygium and change of nail plate form

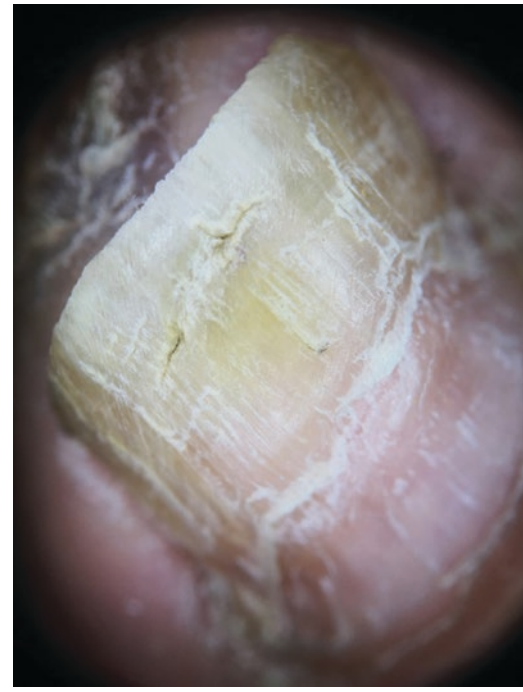

Fig. 11.8 Beau's grooves and onycholysis

at the end of the disease course and are bilateral and symmetrical. However, in patients with tuberculoid leprosy, nail changes usually occur early in the course of the disease and are usually unilateral and asymmetrical [4, 6].

Histopathological examination of the nail bed shows the infiltrate composed of macrophages with a vacuolar cytoplasm, lymphocytes, and plasma cells. Acid-fast bacilli are numerous and responsible for nail bed hyperplasia. This infiltrate, when intense, evolves with epidermal atrophy in both the nail bed and the nail matrix. Thus, it impairs nail plate formation by altering cell differentiation. Nail changes derive from the compressive action of granuloma on the nail bed and matrix [3].

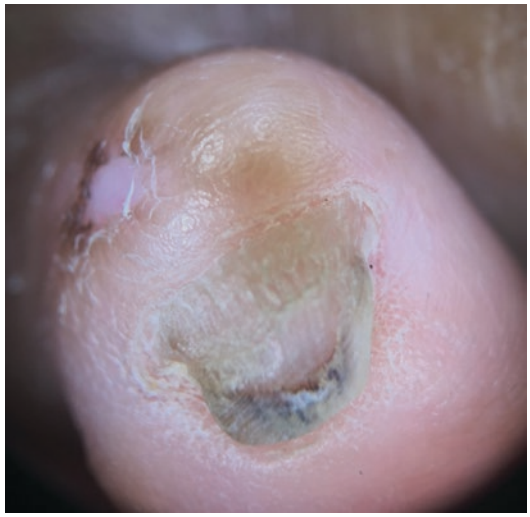

Fig. 11.9 Ulcers on tips of finger, partial onycholysis, and loss of partial nail plate

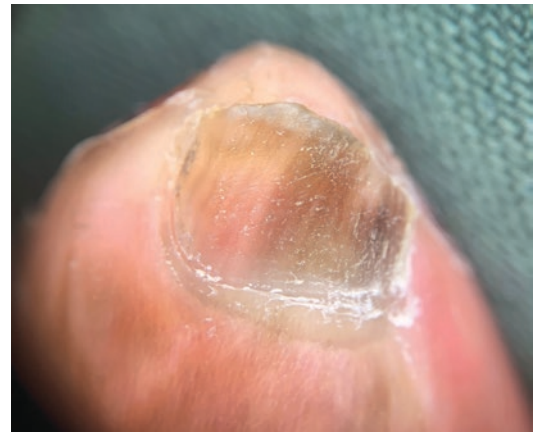

Fig. 11.11 Melanonychia and change of the tips of the fingers

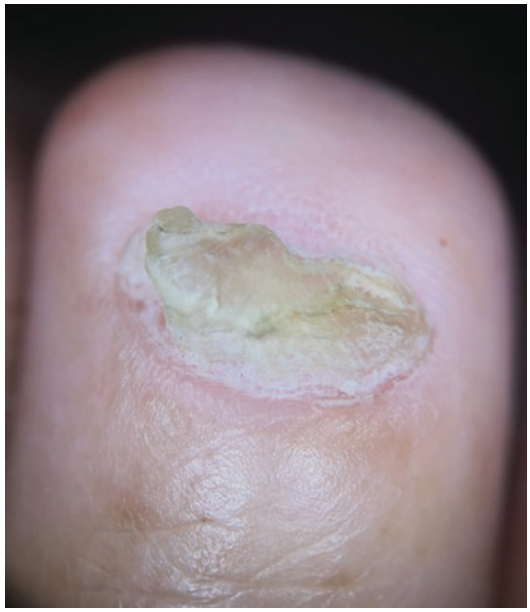

Fig. 11.10 Onychauxis and thickening of the nail

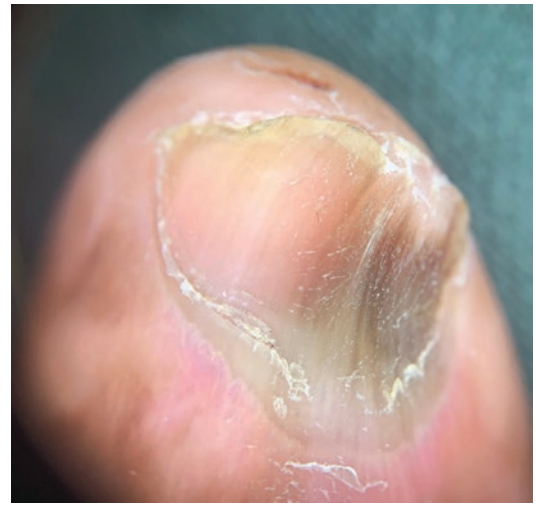

Fig. 11.12 Melanonychia and bulge (pterygium)

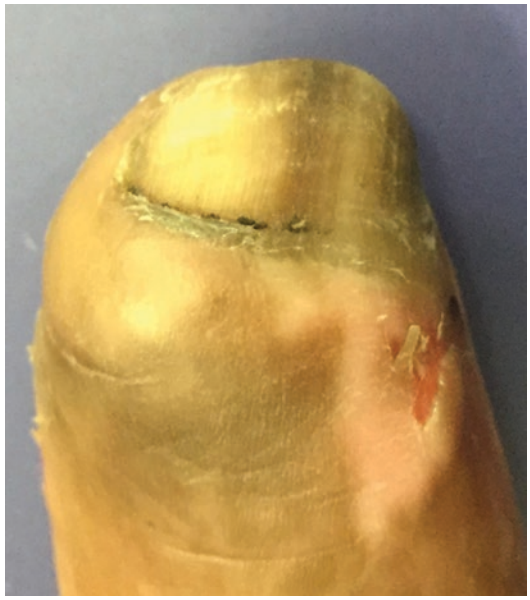

Fig. 11.13 Melanonychia, brachyonychia, resorption of distal phalanges, and skin erosion at the proximal nail fold

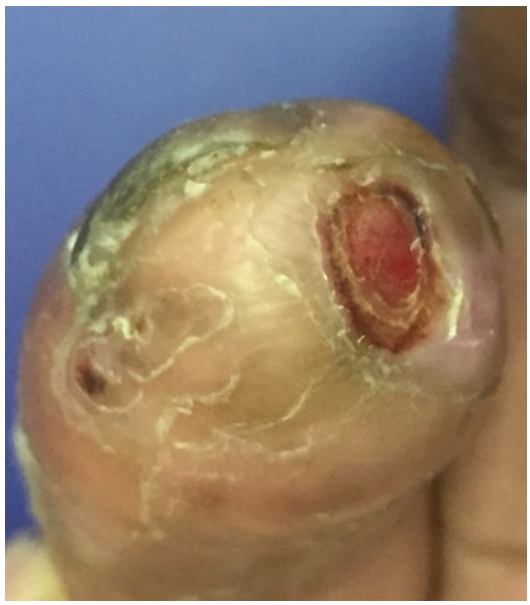

Fig. 11.14 Ulcer on tips of finger

In lepromatous leprosy, it is commonly observed that patients with intense infiltration of the hands do not present nail dystrophies or only lesions in some nails. This is because there are varying degrees of infiltration of the nail dermis. There is only onychodystrophy where the infiltration is intense enough to cause nail bed hyperplasia and matrix compression [3].

Leprosy treatment follows standards set by the World Health Organization. Treatment of onychodystrophies depends on treatment of underlying disease, local trauma care, and control of opportunistic infections [1–3].

It is necessary to consider the pathology of the nails as an important part of leprosy for proper diagnosis and treatment of such a complex disease [1, 2].

Treatment

According to the guidelines development group for the treatment and prevention of leprosy, treatment is the same three-drug regimen with rifampicin, dapsone, and clofazimine for all leprosy patients. Treatment time differs according to leprosy forms with a duration of 6 months for PB leprosy and of 12 months for MB leprosy. Recommended treatment regimens are described in Table 11.2 [17].

The recommendation for rifampicin-resistant leprosy, the guidelines recommend treatment with at least two second-line drugs (clarithromycin, minocycline or a quinolone) plus clofazimine daily for 6 months, followed by clofazimine plus one of these drugs for an additional 18 months.

Nail changes in leprosy are multifactorial and could be related to one or more of the following factors: neuropathy, endarteritis, trauma, drugs, or superimposed infections. The treatment of nail

Table 11.2 Recommended treatment regimens

Age group	Drug	Dosage and frequency	Duration	
			MB	PB
Adult	Rifampicin	600 mg once a month	12 months	6 months
	Clofazimine	300 mg once a month and 50 mg daily		
	Dapsone	100 mg daily		
Children (10–14 years)	Rifampicin	450 mg once a month	12 months	6 months
	Clofazimine	150 mg once a month and 50 mg alternate days		
	Dapsone	50 mg daily		
Children <10 years) or <40 kg	Rifampicin	10 mg/kg once a month	12 months	6 months
	Clofazimine	100 mg once a month and 50 mg twice weekly		
	Dapsone	2 mg/kg/day		

injuries depends on the severity of the alteration caused. The therapeutic direction should prioritize these factors. If these changes are reversed, usually in the early stages of the disease, there is correction of onychodystrophy. If the disease is chronic and the nail changes severe, the chance of improvement becomes smaller [18].

Sporotrichosis

Sporotrichosis is a subacute or chronic infection caused by thermodimorphic fungi of the genus *Sporothrix*. It mostly occurs in tropical and subtropical regions, and it is considered as being the most frequent subcutaneous mycosis in Latin America where it is endemic [19].

The extremities are affected frequently, particularly the hands, including the fingers and the periungual region, and forearms, corresponding to the sites most exposed to trauma.

Sporotrichosis was first described in 1898 by Benjamin Schenck at the Johns Hopkins Hospital in Baltimore, USA. In 1900, Hektoen and Perkins proposed the name *Sporothrix schenckii* for the species described as the genus *Sporothrix* which is the etiological agent of sporotrichosis [20, 21].

Epidemiology and Etiopathogenesis

Due to the fact that the infection results from the agent's inoculation on the skin or mucous membrane by trauma with contaminated plant material, sporotrichosis is recognized as "rose-bush mycosis" or "gardener's mycosis." Cases of zoonotic transmission and rare cases of inhaled infective fungal propagules have been reported, clinically presenting as a systemic mycosis [22, 23].

The zoonotic transmission of sporotrichosis was described involving accidents with various animals like rats, horses, squirrels, armadillos, and cats. The importance of the cat in zoonotic transmission has recently been discussed due to contamination of domestic cats [21, 24–28].

Two important disease transmission routes exist for humans: a sapronotic route involving direct contact with the soil and decomposing organic matter and a zoonotic route in which felines participate actively in the disease transmission. Epidemic control strategies from classic transmission routes required the removal of fungus sources in nature. The horizontal animal transmission (cat to cat), as well as zoonotic transmission, requires the neutering of street animals, treatment of sick cats, education of animal

Fig. 11.15 Cat with multiple sporotrichosis lesions case

owners, and knowledge of aspects of *Sporothrix* transmission. Dead infected animals must be incinerated rather than buried, thus avoiding *Sporothrix brasiliensis* dissemination in the soil and pathogen progression in nature [29, 30] (Fig. 11.15).

Human and animal sporotrichosis have been described worldwide. The incidence of the etiological agents is related to the geographic distribution. In Asia, especially China, *Sporothrix globosa* is estimated to be the etiological agent in 99.3% of human sporotrichosis cases. In other endemic areas, such as Australia and South Africa (94%), also in North America and part of South America (89%), *Sporothrix schenckii* is the predominant species. In South and Southeast Brazilian regions, *Sporothrix brasiliensis* (88%) is the main etiological agent of human and animal sporotrichosis [30–34].

Sporothrix spp. are thermodimorphic fungi, presenting the filamentous form (saprophytic phase) in nature or in vitro at 25 °C and developing yeast-like cells (parasitic phase) in the mammal host or in vitro at 35–37 °C [35].

The virulence profiles change depending on the pathogen characteristics and the host defenses. *Sporothrix brasiliensis* is the most virulent species due to its ability to invade tissue and lead to death, whereas *S. schenckii* has different levels of virulence, and *S. globosa* exhibits little or no virulence [36–38].

Clinical Aspects

Sporotrichosis has diverse clinical manifestations. The most frequent clinical form is the lymphocutaneous form (80%). It appears as a nodular or ulcerated lesion at the site of fungal inoculation and follows a regional lymphatic trajectory, "ascending nodular lymphangitis." The lesions of this lymphatic trajectory are noduloulcerative lesions or "sporotrichotic chancre," which fistula and heal, representing the gumma lesion. The fixed cutaneous form is characterized by nodular, ulcerated, or erythematosquamous lesions located on exposed areas where fungal inoculation occurs [39–41].

The nail unit is susceptible to several minor injuries and may be the site of fungal inoculation. The common forms at this site are the lymphocutaneous form and the fixed cutaneous form. Differential diagnoses include paronychia resulting from injury or infection with *Candida sp*., dermatophytes, *Pseudomonas aeruginosa*, *Streptococcus*, *Staphylococcus,* or herpetic whitlow [42] (Figs. 11.16, 11.17, and 11.18).

The disseminated cutaneous forms have mainly been observed among immunosuppressed patients. Mucosal involvement preferentially affects the ocular mucosa but is not common. Osteoarticular and pulmonary involvement are the most common forms of extracutaneous involvement. However, hematogenous dissemi-

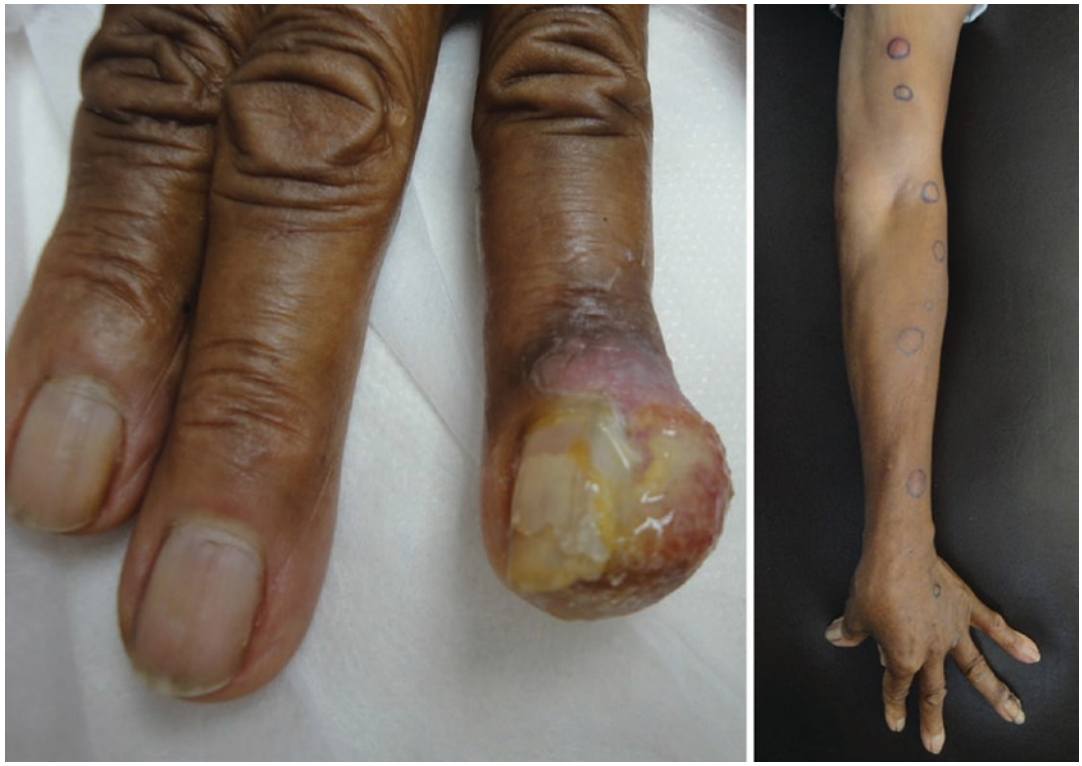

Fig. 11.16 Case 1. Lymphocutaneous form with periungual involvement and nodular lesions at regional lymphatic trajectory

nation with multiple organ involvement may occur at the extracutaneous form [39–41].

Reports of spontaneous regression and the occurrence of hypersensitivity reactions such as nodosum and erythema multiforme may occur [39–41].

The very practical clinical classification is represented at Table 11.3.

Diagnosis

Diagnosis of sporotrichosis at the nail unit is made through the isolation and the identification of the *Sporothrix* species through mycological analysis. It is a simple and low-cost diagnostic method. The samples are collected from the lesion fragment, biopsy, pus, synovial fluid, blood, and cerebrospinal fluid [23, 42].

Direct microscopy (DM) shows several oval structures and yeast-like cells that are in commonly elongated and "cigar shaped." The *Sporothrix spp.* grow in culture media at room temperature (25–30 °C). This species is usually isolated in 4–6 days, for samples collected from skin lesions, and in 10–19 days, for extracutaneous lesions [43–46].

At the histopathology exam, we can observe a diffuse chronic granulomatous dermatitis, the presence of asteroid bodies or Splendore-Hoeppli phenomenon, and the fungal structures. According to the literature, fungal structures are

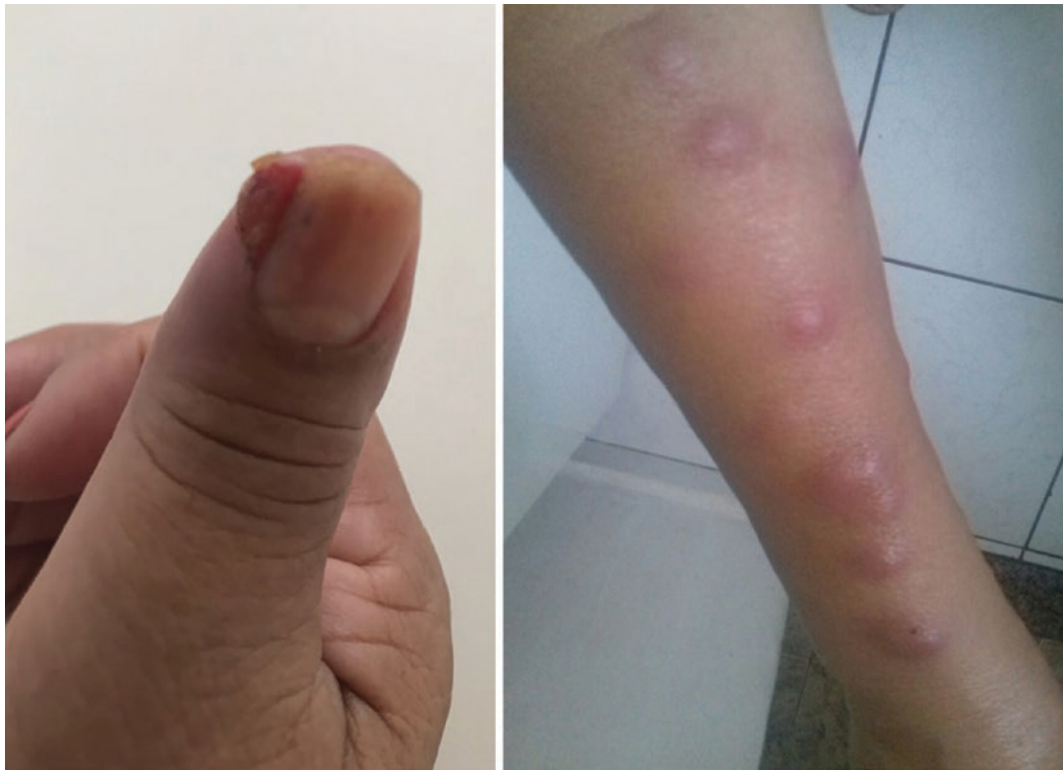

Fig. 11.17 Case 2. Lymphocutaneous form with periungual involvement and nodular lesions at regional lymphatic trajectory

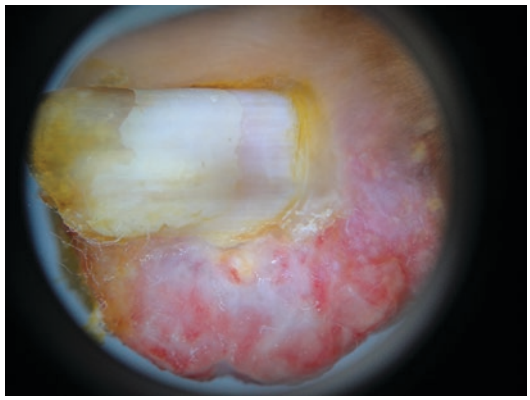

Fig. 11.18 Dermatoscopy of the periungual sporotrichosis lesion

Table 11.3 Clinical classification of sporotrichosis [22, 23]

Skin	Lymphocutaneous Fixed cutaneous Multiple inoculation
Mucous membrane	Ocular Nasal Others
Systemic	Osteoarticular Cutaneous disseminated Pulmonary Neurological Other localizations/sepsis
Immunoreactive	Erythema nodosum Erythema multiforme Sweet's syndrome Reactive arthritis
Spontaneous regression	

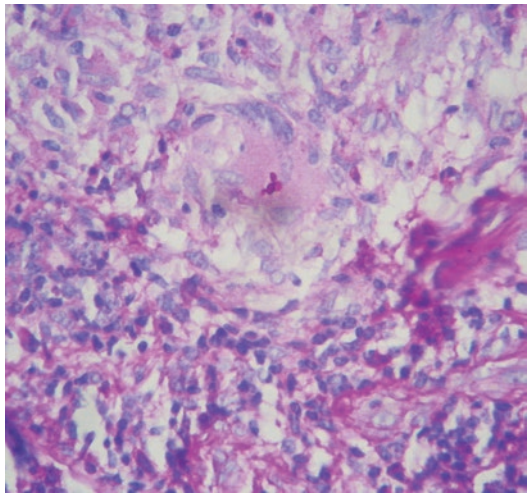

Fig. 11.19 Histopathology staining with H.E. granuloma and neutrophilic inflammatory infiltrate

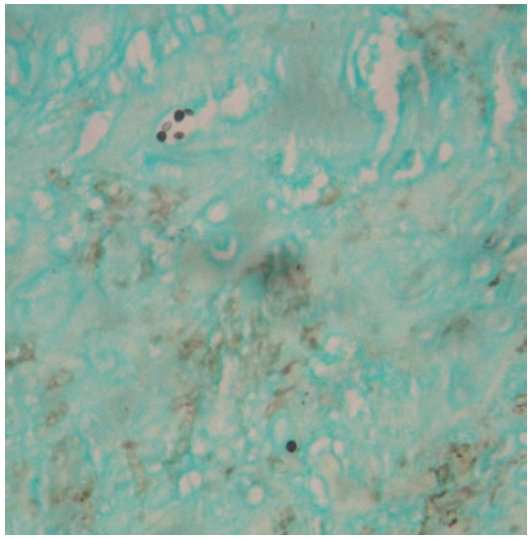

Fig. 11.20 Histopathology with silver staining demonstrating the presence of fungal body

present in 18–35.3% of the cases, depending on the technique [44, 47, 48] (Figs. 11.19 and 11.20).

The serologies, such as immunoenzymatics, especially ELISA (enzyme-linked immunosorbent assay) and Western blotting, are fast and noninvasive tests. They are useful as auxiliary tools for cutaneous forms to diagnose systemic manifestation or atypical forms of sporotrichosis and for screening to control treatment follow-up and drug withdrawal. Other tests are phenotypical identification of the different *Sporothrix* species' DNA sequencing through PCR (polymerase chain reaction) techniques [49, 50].

Treatment

The choice of treatment depends essentially on the clinical form of the disease, the host's immunological status, and the species of *Sporothrix* involved. Itraconazole, potassium iodide, terbinafine, and amphotericin B are the drugs commonly used for treating sporotrichosis.

Itraconazole is considered the drug of choice due to its effectiveness, safety, and posologic convenience with a good scientific evidence level. It is a fungistatic drug that acts by inhibiting the synthesis of ergosterol in the fungus cell wall. It may be used in healthy patients with limited lesions, as well as in immunosuppressed patients and in the systemic form, but not in life-threatening cases of dissemination/sepsis. The main adverse effects are headaches and gastrointestinal disorders. It is hepatotoxic, teratogenic, and embryotoxic. Its greatest disadvantage is the possibility of drug interaction as a consequence of the dependent metabolism on CYP 3A4 common to other several drugs. Complete blood count, biochemistry, and liver function tests should be performed prior to the treatment and after 3–4 weeks [51–53].

Potassium iodide (KI) has been used for treating sporotrichosis since 1903. The mechanism of action is not yet completely understood despite its already known action on the immune response, on destructuring granulomas, on neutrophil chemotaxis, as well as on phagocytosis of *Sporothrix* cells. It is indicated for localized sporotrichosis cases in patients whose immunity is preserved and in immunoreactive forms, such as erythema nodosum or reactive arthritis, due to its immunomodulatory effect. It is contraindicated for patients with thyroid dysfunction, kidney failure, iodine allergy, autoimmune diseases, pregnant and nursing women, deficiency of immune response, and extensive or systemic clinical manifestations. The main adverse events

Table 11.4 Sporotrichosis treatment with the corresponding dosages

Drug	Itraconazole[a] 100 mg CP		Terbinafine 125 and 250 mg CP		Potassium iodide solution
Scheme	Continuous	Pulse	Continuous	Pulse	1.42 g/mL (0.07 g/drop)
Adult	100–400 mg/day[b]	400 mg/day 7 day/month	250–500 mg/day[d]	500 mg/day 7 day/month	2–4 g/day
Pediatric	3–5 mg/kg/day[c]	–	62.5–250 mg/day[e]	–	1–2 g/day
Dosage	AT 1–2 X/day	2 X/day	1–2X/day	1–2X/day	2X/day
Laboratory control[f]	Blood count, biochemistry, and liver function		Blood count, biochemistry, and liver function		Blood count, biochemistry, liver function, TSH, and T4

[a]At mealtime
[b]Start at 100 mg/day
[c]Maximum of 200 mg/day
[d]Start at 250 mg/day
[e]Dose varies according to weight
[f]Prior to treatment, at 3–4 treatment weeks, at the end of the treatment

are metallic taste, nausea, and acneiform eruption. Complete blood count, biochemistry, liver function tests, TSH, and T4 serum levels should be monitored during the treatment [22, 54–56].

Terbinafine is an excellent therapeutic option for patients with contraindications to itraconazole or KI use. It inhibits the synthesis of ergosterol in the fungus cell wall and exhibits fewer drug interactions due to the fact that it is metabolized through the CYP2D6, which is not involved in many other drugs. In addition to this, it is contraindicated for patients with lupus erythematosus and is considered a risk category B drug during pregnancy. Its use has not yet been tested for clinical forms other than the cutaneous. The laboratory exams are the same as those for monitoring the treatment with itraconazole [57, 58].

Amphotericin B is a polyene that links to the ergosterol of fungal membrane, modifying its permeability. When administered intravenously, amphotericin B is cardiotoxic and nephrotoxic, thereby requiring constant evaluation of kidney function and of the serum potassium levels. This is the only drug recommended for pregnant women with severe disease, given that it is not teratogenic [59, 60].

Cryosurgery using liquid nitrogen may be used as a therapeutic complement in refractory cases and in isolated cases of localized lesions in immunocompetent patients. Electrosurgery and surgical removal of small lesions constitute other therapeutic options in selected cases. All therapeutic methods described may be used as monotherapy or as an adjuvant treatment [23].

Sporotrichosis treatment must be maintained until the clinical cure is reached, which usually occurs within 2–3 months. Clinical cure is considered when there is no disease's activity. Systemic forms require longer treatment, ranging from 6 to 12 months [41, 51].

Table 11.4 indicates the main drugs used in sporotrichosis treatment with the corresponding dosages [41, 61].

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Latest Research in Nail Psoriasis

12

Marcel C. Pasch and Matilde Iorizzo

Abbreviations

AMP:	Antimicrobial peptide
HLA:	Human leukocyte antigen
hβD:	Beta defensin
IFN:	Interferon
JAK:	Janus kinase
miRNA:	microRNA
NAPSI:	Nail Psoriasis Severity Index
N-NAIL:	Nijmegen-Nail psoriasis Activity Index tooL
OCT:	Optical coherence tomography
PASI:	Psoriasis Area Severity Index
PD:	Power Doppler
PDE4:	Phosphodiesterase type 4
PDL:	Pulsed dye laser
PGA:	Physician global assessment
QoL:	Quality of life
RCT:	Randomized controlled trial
TI:	Triamcinolone acetonide iontophoresis
TNF:	Tumor necrosis factor
US:	Ultrasonography
UTR:	Untranslated region

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About half of the patients who suffer from psoriasis also have changes affecting their nails. Psoriatic nail disease differs greatly in clinical appearance, severity, and impact for individual patients. It is associated with significant pain and physical impairment as well as issues such as self-image and cosmetic concerns, difficulty with tasks involving manual dexterity, anxiety and/or depression, an increased number of missed workdays relative to patients without nail involvement, and substantial impairments in quality of life [1]. With hundreds of publications each year, nail psoriasis is without any doubt the topic in onychology with the greatest interest of the scientific community. This interest can be explained by the major physical and emotional impact it has, its relation with psoriatic arthritis, progress in diagnostic tools and procedures, and the introduction of new treatments. This chapter highlights many new insights by discussing recent advances within the context of our previous general understanding of this particular expression of psoriasis, which can be found in several comprehensive and excellent publications [2–4].

Epidemiology

The prevalence of plaque psoriasis varies between 0.7% and 2.9%, with a preference for the Caucasian population [5, 6]. Other common expressions of psoriasis may affect the scalp,

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joints, creases, genitals, or nails and occur even in patients without psoriasis of the skin. Among plaque psoriasis patients, prevalence of nail psoriasis is over 50%, with an estimated lifetime incidence of 80–90% [7, 8], though the patient-reported incidence sometimes is lower [9]. Twenty-seven percent of nail psoriasis is localized only in fingernails and 16% only on toenails. In the remaining 57% of the patients, both fingernails and toenails are involved [8].

Who are patients at risk to develop nail psoriasis? Nail psoriasis has the highest prevalence in patients between 35 and 64 years of age and is much rarer in children [10–12]. Psoriasis patients with psoriatic arthritis have increased risk to develop nail psoriasis, and nail psoriasis seems to be more severe in psoriasis patients with psoriatic arthritis [13]. Nail involvement may be present in >80% of psoriatic arthritis patients [14] and is considered an indicator for patients at risk for future psoriatic joint damage [15]. Also, patients with genital psoriasis have an increased prevalence of nail involvement [16, 17]. Nail psoriasis in the absence of cutaneous or joint disease is present in 5–10% of psoriatic patients [18]. A recent study from Germany found a higher prevalence (58% vs. 44%) and severity of nail psoriasis (7.4 vs. 5.3 involved fingers) among psoriasis patients consuming tobacco than among nonsmoking psoriasis patients [19]. An explanation for more nail involvement could be the higher PASI among smokers than among nonsmokers. Also psoriatic arthritis was found more frequently in nonsmokers than in smokers. Finally, patients with nail psoriasis are significantly less likely to have itch all or most of the time than other psoriasis patients [20].

Pathophysiology

Environmental factors, genetic susceptibility, abnormal function of keratinocytes, and immunological disturbances of the innate and acquired immune system are all postulated to play a role in the pathophysiology of psoriasis in which inflammation and epidermal hyperproliferation are fundamental processes [21, 22]. While the role of environmental factors other than smoking is completely obscure in the pathogenesis of nail psoriasis, some data are available on genetic susceptibility. Genome-wide association studies have linked chromosomal loci PSORS1 through PSORS9 to plaque psoriasis. PSORS1, containing the allele for human leukocyte antigen (HLA) Cw6, appears to be of major importance in plaque psoriasis. However, patients with nail psoriasis and/or psoriatic arthritis are more frequently HLA-Cw6 negative, indicating a separate genotype [23, 24]. Nail involvement appears to be also milder in HLA-Cw6-positive than in HLA-Cw6-negative psoriasis patients [24]. A different genotype of psoriasis patients with nail involvement is also indicated by the finding that these psoriasis patients more often (50.7%) have a positive family history for psoriasis or psoriatic arthritis than psoriasis/psoriatic arthritis patients without nail involvement (29.6%) [25]. In Asian patients, the Nail Psoriasis Severity Index (NAPSI) was significantly higher in HLA-B46-positive patients [26]. A study from Singapore observed an association between nail psoriasis and HLA-A*02:07 carriers, HLA-B*46:01 carriers, and HLA-C01*02 carriers, whereas C*6:02 carriers were less prone to have nail involvement [27].

Both the innate and adaptive immune system but also skin barrier function proteins have been identified to play a role in the pathogenesis of psoriasis [28–30]. A recent case report has put attention to a potential role of epidermal mast cells in the nail matrix [31]. An increased number of mast cells, belonging to the innate immune system, was identified below and within the nail epithelium. These mast cells may contribute to the pathogenesis of nail psoriasis by T-cell activation and angiogenesis via mast cell-derived cytokines such as IFN-γ and IL-17 [32].

Antimicrobial peptides (AMPs) are small molecules with a broad spectrum of innate defense properties. AMPs may also play a role in the nail unit as the nail appears to be capable of ensuring efficient innate immune defense despite persistent exposure to bacteria and fungi. In psoriatic skin plaques, the levels of several AMPs are reported to be highly upregulated [33]. The AMP profile, specifically the presence and distribution

of cathelicidin (LL-37) and beta defensins (hβD-2, hβD-3, and hβD4), in normal nails and in psoriatic nails has also been investigated [34]. LL-37-positive cells were present throughout the nail unit, but in psoriasis-affected nails, much more LL-37-positive cells were observed in the epithelial layer of the nail bed than in the control group. Also, higher numbers of cells positive for hβD-2 and hβD3 were observed in nail bed epithelia of psoriatic nails. Cells positive for hβD-4 staining were not observed in either psoriatic or control group nails. The authors suggest that LL-37 is characteristic for nail psoriasis and speculate that LL-37 may be of particular importance for the psoriasis-related inflammation in the nail unit due to either excessive or perpetual exposure of the nail apparatus to microbial and fungal agents. Furthermore, LL-37 is not solely an AMP, but LL-37 can also be complex with self-DNA and RNA, and this complex is assumed to play an important direct role in the pathogenesis of psoriasis by activation of dendritic cells to self-antigens followed by involvement of the adaptive immune system [35, 36]. Activated dendritic cells produce numerous cytokines, including IL-12 and IL-23. IL-23 binds to the IL-23 receptor and promotes T cells of the Th17 class to expand. On the other hand, IL-12 acts on T cells to induce the Th1 class of T cells to expand. Th17 class T cells produce inflammatory cytokines including IL-17A, IL-17F, IL-22, IL-26, IL-6, IL-21, TNF-α, and IFN-γ. Ventura et al. suggest an important role for candida as trigger for nail psoriasis through the LL-37 pathway [37]. Candida could activate LL-37 resulting in the abovementioned loop with induction, maintenance, and exacerbation of clinical nail psoriasis as the final step.

To evaluate the inflammatory micromilieu in psoriatic nails, the expression of several mediators that have been already identified in psoriatic skin plaques has been analyzed: IL-6, IL-8, TNF-α, NF-kB, and IL-10 [32]. Similar to psoriatic skin, increased TNF-α, IL-6, IL-8, and NF-kB was demonstrated in psoriatic nails. TNF-α, IL-6, and IL-8 are proinflammatory cytokines which appear to contribute to the inflammatory reaction in the nail unit. NF-kB is a protein complex that controls transcription of DNA, cytokine production, and cell survival. It is of special interest due to phosphodiesterase type 4 (PDE4) inhibitor such as apremilast that, among other pathways, is known to be involved in the modulation of inflammatory signaling via NF-kB. In contrast with psoriatic skin where IL-10 is low, pronounced IL-10 staining was found in the nail bed with an increase in psoriasis-affected nails. IL-10 is an anti-inflammatory cytokine with regulatory and inhibitory properties on proinflammatory responses of T cells and keratinocytes. The presence of the anti-inflammatory cytokine IL-10 may confirm the nail unit as a site of assumed relative immune privilege.

A role for the nervous system and neuropeptides in development of nail psoriasis was suggested by Kecici et al. [38]. They report a patient with a traumatic injury of an arm many years before, resulting in permanent axonal and demyelinating neuropathy of the right median and ulnar nerve. He presented with nail psoriasis of his fingers and toes, but severity of nail psoriasis was much less in the second to fifth finger of the denervated hand. Nail psoriasis was present in the first finger which has double innervation by both the median and the radial nerve. Three neuropeptides, substance P, nerve growth factor, and calcitonin gene-related peptide, have been identified in association with the IL-23-driven pathogenesis of psoriasis [39]. Remission of the lesions after nerve injury may be due to decline in these neurotransmitters, which primarily influence inflammation and epidermal hyperplasia.

Clinical Features

The inflammatory reaction in nail psoriasis can be present in the nail matrix and/or in the nail bed. Clinical manifestations differ according to which of these structures is involved within the nail apparatus. Psoriasis of the nail matrix can cause pitting, leukonychia, red spots of the lunula, Beau's lines, thickening, and crumbling of the nail plate (Fig. 12.1a–e). The pits typically are relatively large, deep, and irregularly

distributed. Psoriasis of the nail bed presents as oil-drop discoloration, splinter hemorrhages involving the distal third of the nail plate, subungual hyperkeratosis, and/or onycholysis (Fig. 12.1f–h). A clue to the diagnosis of psoriasis as the cause of onycholysis is the characteristic salmon-colored zone at the leading edge of onycholysis (Fig. 12.1f). Nail folds may also be affected by psoriasis and manifest with papulosquamous or pustular lesions or with paronychia as result of psoriatic inflammation of the periungual region (Fig. 12.2). Subungual hyperkeratosis and nail fold psoriasis are associated with the severity of both nail psoriasis and cutaneous psoriasis [40].

Recent publications on clinical aspects of nail psoriasis have brought new data on several clinical signs of psoriatic nail disease. The value of leukonychia as expression of nail psoriasis is under discussion because a gender- and age-matched case-control study suggested that leukonychia is not more frequent in nail psoriasis than in controls [41]. However, in another study, punctate leukonychia was rather suggestive for psoriasis and alopecia areata [42]. Some less known signs of nail psoriasis got more attention recently. Longitudinal ridges (Fig. 12.3) do not belong to the classical features of nail psoriasis but occur significantly more often in patients than in control subjects [41], which was confirmed by a prevalence of longitudinal ridging in 36.9% in a huge cohort of Chinese patients with nail psoriasis [43]. The development of koilonychia in psoriasis is rare and may be the consequence of nail bed hyperkeratosis that places pressure on the central distal matrix, thus inducing the spoon-shaped abnormality [44]. While pitting probably is the best-known sign of nail psoriasis, an intriguing variant of pitting, called "pseudo-pitting," was published by Di Chiacchio et al.

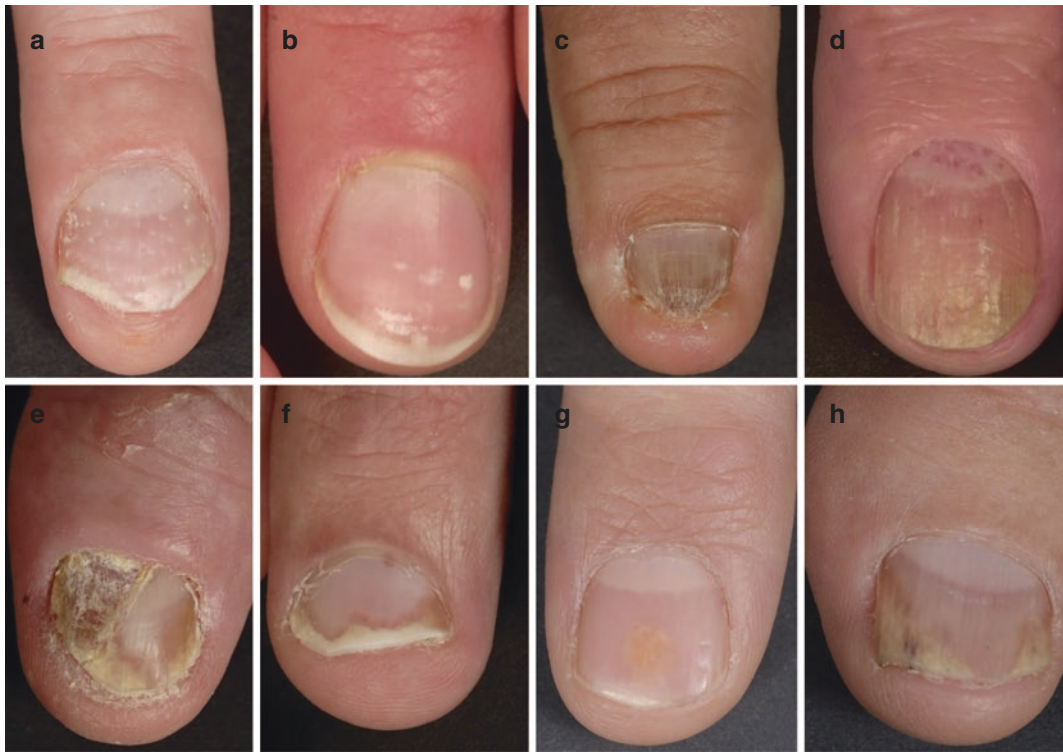

Fig. 12.1 Psoriasis of the nail matrix can cause pitting (**a**), leukonychia (**b**), thickening (**c**), red spots of the lunula (**d**), and crumbling of the nail plate (**e**). Psoriasis of the nail bed presents as onycholysis (**f**), oil-drop discoloration (**g**), and splinter hemorrhages involving the distal third of the nail plate often embedded in subungual hyperkeratosis and/or onycholysis (**h**)

Fig. 12.2 Nail folds may also be affected by psoriasis and manifest with papulosquamous or pustular lesions or with paronychia as result of psoriatic inflammation of the periungual region

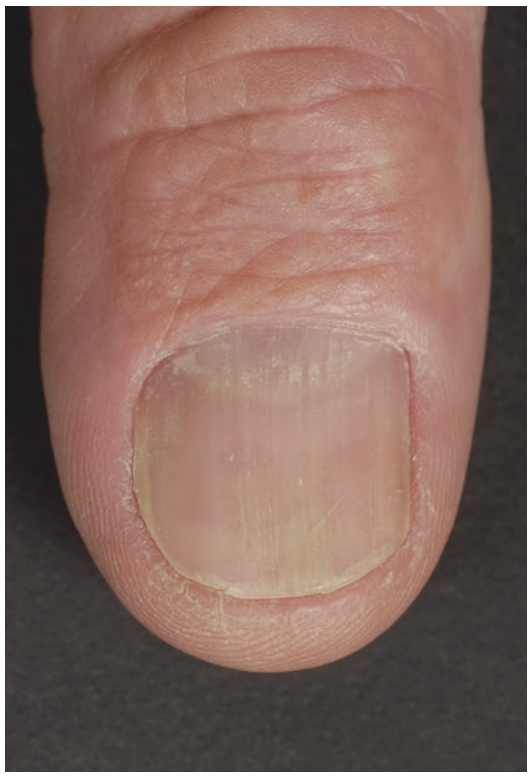

Fig. 12.3 Longitudinal ridges do not belong to the classical features of nail psoriasis but are significantly more frequently seen in patients than in control subjects

[45]. They presented a patient with pits overlying salmon-colored patches (Fig. 12.4). Interestingly, these pits were only observed above the salmon

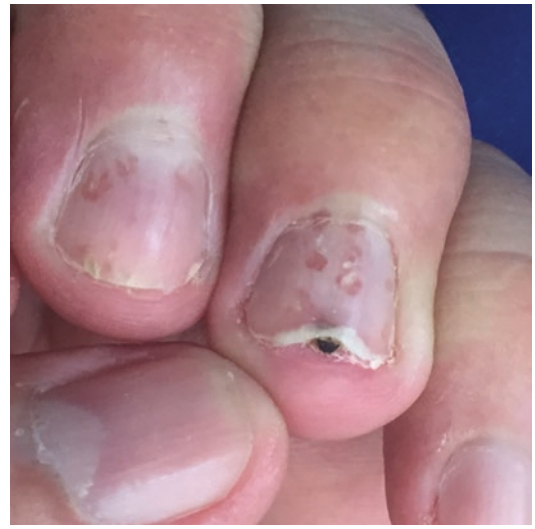

Fig. 12.4 Pseudo-pitting in nail psoriasis, presenting with pits overlying salmon-colored patches [45]

patches and not elsewhere on the nail plate. Histopathology of the nail bed showed typical psoriasis with dilated capillaries in the papillary dermis responsible for the orange discoloration and parakeratosis with accumulation of neutrophils in the overlying nail plate that could explain the formation of pits.

A recent study investigated and compared nail signs in plaque psoriasis patients and in psoriatic arthritis patients as an attempt to identify nail findings to discriminate between psoriatic arthritis patients and psoriasis patients without arthritis [46]. Transverse grooves (Beau's lines; Fig. 12.5) were seen five times more often in patients suffering from psoriatic arthritis than in patients with just skin involvement. Also, onycholysis and splinter hemorrhages occurred more often in psoriasis patients with arthritis. Hence, the presence of Beau's lines, onycholysis, and splinter hemorrhages may early identify psoriatic arthritis patients and thus help to recognize patients at risk of developing destructive joint damage. The clinical relevance of this still has to be proven because Beau's lines may also just reflect the impact of the arthritis-/enthesitis-induced inflammation on the nail matrix.

In general, nail psoriasis is a clinical diagnosis. The main differential diagnosis is onychomy-

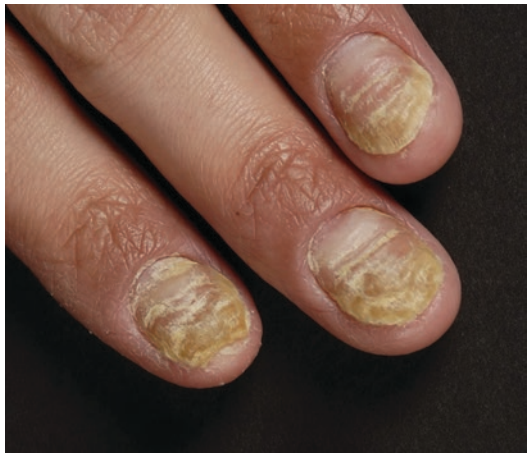

Fig. 12.5 Transverse grooves (Beau's lines) are seen more often in patients suffering from psoriatic arthritis than in patients with just skin involvement and may also be associated with distal interphalangeal arthritis and enthesitis [46]

cosis, but other inflammatory nail disorders, like lichen planus, and also contact allergy should be considered. Nail abnormalities mimicking nail bed psoriasis were recently reported in two patients using nail hardeners [47]. The assumed mechanism was a contact allergy caused by the high level of the hardening substance formaldehyde in the formulation. Features of nail psoriasis, including onycholysis and severe subungual hyperkeratosis, have also been reported in patients wearing acrylic nails [48]. These patients had positive patch testing to methyl methacrylate, suggesting that acrylate sensitization can cause these pseudo-psoriatic nails.

Nail Psoriasis and Onychomycosis

Both onychomycosis and nail psoriasis are very common nail disorders, share many clinical signs, and affect the same digits, thus making the differential diagnosis difficult. Furthermore, nail involvement in psoriasis patients is assumed to be a risk factor to develop onychomycosis. Because of all these reasons, it is useful to exclude onychomycosis and associated onychomycosis in all patients presenting with psoriasis-like nail signs. The many interesting questions arising from the close affinity of these two diseases have been discussed by Rigopoulos et al. [49]: Can nail psoriasis really predispose to onychomycosis? Can onychomycosis exacerbate psoriasis through a Koebner phenomenon? Does psoriasis treatment contribute to this association? The authors theorize that a decreased incidence or at least not a higher incidence of onychomycosis in nail psoriasis would have been likely. Changes in the protective function of the normal orthokeratotic nail plate may increase the risk on onychomycosis, but the increased nail growth in psoriasis and the high levels of AMPs in the skin and nail in psoriasis, such as cathelicidin (LL-37), could be protective. However, the net effect of protective and predisposing factors for onychomycosis in psoriatic nails appears to be a higher incidence of onychomycosis. According to systematic reviews, 10–18% of psoriasis patients suffer from onychomycosis compared to a prevalence of 9% in control groups or 3% in the general population [50, 51]. Onychomycosis not only occurs more often in psoriasis patients; the general assumption that patients with severe nail psoriasis more often have onychomycosis than patients with mild nail psoriasis could also be confirmed [52]. Several studies have indicated that psoriasis patients more often suffer from an onychomycosis caused by a yeast than patients without nail psoriasis [51, 53], though this could not be confirmed by a systematic review from 2014 [50]. A recent retrospective Italian study among 711 psoriasis patients and 8570 non-psoriasis patients even found significantly more yeast infections in non-psoriasis patients (50.4%) than in psoriasis patients (43.6%) with onychomycosis [54].

The question whether onychomycosis acts as Koebner phenomenon and exacerbates nail psoriasis is answered in a positive way by Rigopoulos et al. in their review [49]. The same was concluded true for the question if treatment of nail psoriasis may influence the incidence of onychomycosis: Extensive use of topical corticosteroids locally applied to treat nail psoriasis seems to be a factor facilitating fungal infections due to their immunosuppressive effects. Also, conventional systemic treatments cyclosporine and methotrexate alter the immune status and could possibly

lead to vulnerability for onychomycosis. Increased incidence of onychomycosis in nail psoriasis patients on a biologic has also been reported. The incidence in psoriatic patients with nail disease receiving 24 weeks of treatment with an anti-TNF-α drug was 20.3% compared to 13.9% of controls [55]. The risk was in particular increased for infliximab (33%) but not for etanercept (13.3%) and adalimumab (15.5%). Bigger differences were reported from a smaller Polish study with 24 nail psoriasis patients with onychomycosis: Nail fungal infections were more common in psoriatic patients receiving systemic treatment compared to these treated exclusively with topical agents (75% vs. 25%, respectively; $p = 0.005$) [56].

Many hypotheses have been formulated to explain higher rates of onychomycosis in nail psoriasis [50]. It is hypothesized that morphological abnormalities in psoriatic nails are predisposing factors for onychomycosis and vice versa. In healthy nails, the compact orthokeratotic nail plate and hyponychium act as a natural barrier preventing the development of fungal infections, which may be disturbed in abnormal nail plates in diseases such as nail psoriasis. It appears that the genetic-determined immunological makeup may also play a role in the increased susceptibility for onychomycosis of nail psoriasis patients: The role of the HLA class II phenotype has been studied in a prospective case-control of patients with nail psoriasis with onychomycosis (cases) and without onychomycosis (controls) [57]. HLA-DR * 08 and HLA-DR * 01 probably increase the susceptibility to fungal infection in psoriasis-affected nails. However, these HLA class II alleles are not known to be more present in patients with nail psoriasis than in controls, so this does not fully explain a potential increased prevalence of onychomycosis among patients with nail psoriasis.

The clinical consequence of the relatively high prevalence of onychomycosis in nail psoriasis may be a strengthened general advice to rule out onychomycosis or concomitant onychomycosis in these patients.

Drugs as Inducers of (Nail) Psoriasis

Antimalarials (chloroquine and hydroxychloroquine), beta-blockers, and lithium are best known as inducers of psoriasis. Many other drugs have also been shown to be able to induce plaque psoriasis and nail psoriasis (Box 12.1) [58]. Recent publications pointed also to other drugs as inducers of nail psoriasis. It has been reported that paradoxical side effect of anti-psoriasis biological therapies, which were known from anti-TNF substances, may also be seen with anti-IL-17 biologics, like ustekinumab and secukinumab [59]. Teriflunomide, the active metabolite of leflunomide and used as an immunomodulatory agent in multiple sclerosis, and nivolumab, a monoclonal antibody against the programmed cell death protein 1 (PD-1), were recently also reported to induce nail psoriasis, in particular nail bed psoriasis [60–62].

Box 12.1 Drug-Induced Psoriasis [58–61] Republished with Permission of John Wiley and Sons Publisher

Associated agents

- Antimalarials (chloroquine and hydroxychloroquine)
- Beta-blockers
- Lithium

Likely associated agents

- Angiotensin-converting enzyme inhibitors
- Antibiotics (penicillins, tetracyclines, sulfonamides)
- Corticosteroids (withdrawal)
- Imiquimod
- Interferons
- Nonsteroidal anti-inflammatory agents
- Terbinafine

Less commonly reported agents

- Acetazolamide
- Amiodarone
- Anti-PD1 immune checkpoint inhibitor

- Benzodiazepines
- Bupropion
- Calcium antagonists
- Carbamazepine
- Cimetidine
- Clonidine
- Digoxin
- Dihydropyridine
- Fluoxetine
- Gemfibrozil
- Gold
- IL-17 blocking biologics
- Mercury
- Morphine
- Nivolumab
- Olanzapine
- Progesterone
- Quinidine
- Ranitidine
- Rituximab
- Teriflunomide
- TNF-α inhibitors
- Valproic acid
- VEGF antagonists

Metabolic Syndrome

Psoriasis is a chronic immune-mediated disorder. The systemic nature of the inflammatory process involved in its etiopathogenesis is responsible for several comorbidities, which themselves have a considerable impact on the patient's quality of life and mortality. It has been shown that patients with psoriasis are more likely to have metabolic syndrome [63]. Metabolic syndrome is a systemic proinflammatory state and, therefore, a cluster of several well-known cardiovascular risk factors that include abdominal obesity, atherogenic dyslipidemia, hypertension, and insulin resistance. Involvement of the nail appears not to change the risk to develop metabolic syndrome as was shown in a case-control study [64]. Also, a subgroup analysis in a systematic review on 32 publications on cardiovascular disease and/or risk factors in psoriatic arthritis concluded that nail involvement does not increase risk on development of metabolic syndrome [65].

Quality of Life

Skin diseases frequently have significant negative impact on patients' psychological well-being. Psoriasis on visible areas of the skin may have a substantial negative impact on quality of life (QoL) [66, 67]. Not only the visibility of nail psoriasis is responsible for the impact on QoL but also pain, inability to grasp small objects and to tie shoelaces or button clothes, and an altered sense of fine touch play a role in this. Internalized stigma may be one of the major factors responsible for the psychosocial burden of nail psoriasis because fingernail psoriasis turned out to be related with the level of internalized stigma in psoriasis patients [68], although another study could not confirm this [69].

Cutaneous conditions may also have adverse effects on intimacy. A dermatologic intimacy scale has been created to assess the impact of skin disease on intimacy [70]. Patients with genitalia, nails, face, neck, and scalp involvement had greater impairment of intimacy than patients without involvement of these areas of the skin.

The impact of nail psoriasis on QoL was reported from several continents and cultures [1, 71]. In a Lithuanian survey among 385 psoriasis patients, only 4.1% of the respondents stated that psoriasis-related nail damage had no effect on their quality of life [72]. Already in 1996, De Jong et al. reported that 93% of patients suffering from nail psoriasis consider it a serious cosmetic handicap [73]. Later, it was reported that fingernail psoriasis has an additional negative impact on the QoL in psoriasis patients, particularly in patients with both nail matrix and nail bed signs of the disease [1, 74]. QoL is worse in patients with only nail bed alterations than in patients with only nail matrix features. Possibly, this is caused by the fact that most nail plate changes can be covered with nail polish, in contrary to hyperkeratosis which remains visible and may be painful.

Recent studies on QoL in psoriasis have shown that nail involvement belongs to the strongest predictors of reductions in health-related QoL, measured by several tools, like the Dermatology Life Quality Index (DLQI), Short Form 36 Health Survey (SF-36), and EQ-5D [9, 71, 72, 75–79]. Contrary to most plaque psoriasis patients, who expected improvement in their QoL, patients with nail involvement were prone to expect decline within 6 months [79]. In conclusion, nail psoriasis has major impact on physical and mental aspects of QoL, and this should be a matter of discussion during consultations with patients suffering from nail psoriasis or even nail disease in general.

Nail Psoriasis in Children

While about half of adults with skin psoriasis have nail involvement, this is rather uncommon in children. In particular, in infants with guttate or plaque psoriasis, prevalence is relatively low (12.5–19%) [11, 12, 80, 81]. Prevalence in adolescents was reported to be 38% and is approaching the prevalence of adult patients [81]. A retrospective study from Mexico reported a lower prevalence of 5% in children and adolescents in the central American region [82]. Pitting and onycholysis associated with subungual hyperkeratosis are the most common signs, which is not different from adults [11, 81]. Nail plate thickening involving several toenails that are difficult to trim is a common sign of presentation of nail psoriasis at a very young age.

It was assumed that severity of nail psoriasis in childhood does not correlate with that of the skin psoriatic lesions [11]. However, a recent multicenter study showed a positive correlation between severity of nail and skin involvement [81]. The same study showed an association between nail psoriasis and psoriatic arthritis in children. Furthermore, nail psoriasis might be a potential clinical predictor for a more severe disease course over time in children with psoriasis [12].

Pathology

Histologically, psoriasis of the nail folds simulates psoriasis involving other cutaneous sites. Histopathologic features of nail bed and matrix psoriasis are somewhat different from psoriasis elsewhere on the body [83]. In psoriasis involving the nail bed and matrix, the following histologic features are characteristic: varying degrees of uniform hyperplasia, spongiosis, appearance of a granular layer, spongiform pustules, and parakeratosis with neutrophils [7]. Unlike psoriasis elsewhere, nail bed and matrix histopathology reveal hypergranulosis in more than half of the cases.

Biopsies taken from the nail bed are more helpful when subungual hyperkeratosis is present, but areas of onycholysis generally do not produce useful histologic information [84]. In a histological nail bed study, the feature found most frequently was hyperkeratosis with parakeratosis (78% of biopsies), followed by neutrophilic infiltration of nail bed epithelium (63%), hypergranulosis (58%), psoriasiform hyperplasia (53%), dilated capillaries (47%), and serum exudates in 43% of cases [85]. Less frequent findings seen were melanin pigment in 28%, acanthosis in 23%, and hemorrhages in 22%.

The use of nail clipping microscopy as a diagnostic tool for nail psoriasis has shown that the predominant histologic features consistent with psoriasis are a thickened nail plate, subungual hyperkeratosis, neutrophils, and parakeratosis [86–90]. Hyperkeratosis between plate and subungual region can be seen in mounds, reminiscent of arches, and not in a continuous fashion along the undersurface of the nail [86]. Also, serous lakes, bacteria, and blood collections are frequent findings [86]. Clinically normal-looking nails in patients with psoriasis can present microscopic abnormalities [86]. The histology of the nail clipping is similar in the presence or absence of arthritis [87].

Histologic features reminiscent of psoriasis in nail clippings and nail soft tissues can be seen with onychomycosis, making it important to

evaluate for the presence of fungal elements with a histologic stain for fungus, such as a periodic acid-Schiff (PAS) stain. Of course, presence of onychomycosis does not exclude concomitant psoriasis because nail psoriasis is a risk factor for onychomycosis. Nevertheless, it might be possible to differentiate nail psoriasis from onychomycosis in nail clippings even without a fungal staining: In the subungual region of onychomycosis, serous lakes, neutrophils, and number of layers of parakeratosis are more intense than in psoriasis [91]. Bacteria are more frequent in psoriasis, and the nail transition zone is more commonly blurred and irregular in onychomycosis.

Noninvasive Diagnostic Techniques

Making the diagnosis of nail psoriasis is not always easy, in particular in patients without skin or joint involvement. General accepted criteria for the diagnosis of nail psoriasis do not exist, and the diagnosis is primarily based on clinical signs. Additional tests to confirm clinical suspicion often are essential because other inflammatory nail disorders or onychomycosis may mimic nail psoriasis clinically. A nail unit biopsy taken from the affected area of the nail unit may be considered golden standard, but also noninvasive techniques like dermoscopy and ultrasound have well-described features. Other noninvasive imaging techniques, such as magnetic resonance image techniques or optical coherence tomography, have also been introduced to facilitate the diagnosis of nail psoriasis.

Dermoscopy

Dermoscopy of the nail unit (onychoscopy) can be used to evaluate the nail plate surface, the free edge, and the periungual tissues. A systematic review on onychoscopic features of nail psoriasis was published recently [92]. Coarse pits/pitting constitutes the most common onychoscopic feature (Fig. 12.6a). Other onychoscopic features of nail matrix psoriasis are nail plate thickening, trachyonychia, transverse grooves, leukonychia, and red spots in the lunula (Fig. 12.6b). The most common onychoscopic feature indicating nail bed involvement is splinter hemorrhages, appearing as thin, longitudinal lines as a sign of capillary bleeding (Fig. 12.6c,d). Other nail bed features of nail psoriasis are salmon patches, onycholysis, dilated globule vessels, streaky capillaries, and subungual hyperkeratosis. A recent observational study from India confirmed a publication of Iorizzo et al. that the most common onychoscopic findings in psoriasis are not pitting or splinter hemorrhages but dilated and tortuous capillaries in nail bed and hyponychium, present in 90% of patients [93, 94]. Hashimoto et al. added erythematous borders of an onycholytic area and agminated capillary dots as additional features of nail bed psoriasis and concluded that changes in erythematous borders of an onycholytic area may reflect disease activity [95]. Agminated capillary dot is a finding that refers to capillary dilatation of the nail bed and manifests as red dots and globules. Yadav and Khopkar described bright-red- to dusky-colored dilated vessels arranged parallel over the onychodermal band of the nail plate [96]. They appear as fusiform dilatation surrounded by a prominent halo and were found more often in psoriasis patients than in normal controls.

Dermoscopy has also been investigated as a tool to differentiate between psoriatic arthritis and rheumatoid arthritis [97]. Possible dermoscopic differences in vascular appearance of the nail fold in these two conditions were investigated. Regarding the vascular appearance in psoriatic arthritis *sine* psoriasis and rheumatoid arthritis, the presence of diffuse reddish background with or without sparse dotted vessels was suggestive for psoriatic arthritis, whereas parallel dotted/short linear vessels (“fish school-like” pattern) or irregular/ramified, blurry, purple vessels were suggestive for rheumatoid arthritis.

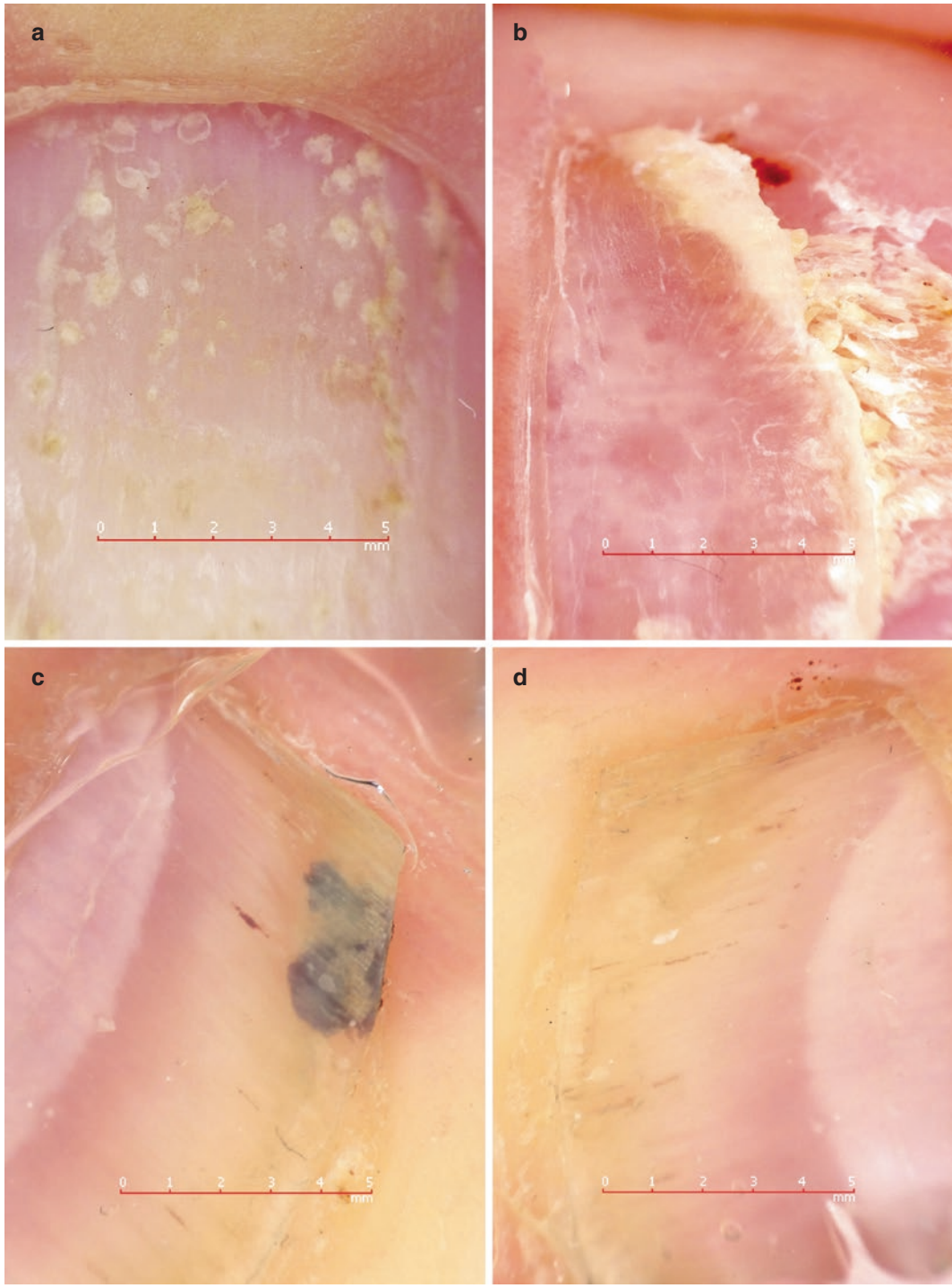

Fig. 12.6 Dermoscopic features of nail psoriasis: pitting (**a**), red spots of the lunula (**b**), and splinter hemorrhages involving the distal third of the nail (**c**, **d**)

Ultrasound

High-frequency B-mode ultrasonography (US) and power Doppler (PD) study can reveal changes in nail anatomy and vascularization in patients with nail psoriasis. Ultrasonographic examination of a nail makes it possible to visualize the nail plate (three-layer structure with two hyperechoic bands bordering an almost anechoic space), the matrix at the base of the nail (isoechoic), and the nail bed (hypoechoic) in B mode, as well as local microvascularization (of matrix and bed) in PD. To adequately visualize the nail structure, a high-frequency probe is needed. A frequency above 18 MHz can provide an accurate imaging definition of the nail and enthesis complex [98].

An issue on the use of US in psoriatic nail disease is the lack of standardization and validation in the scanning technique as well as in the interpretation of findings. Regarding the nail plate in nail psoriasis, four types of morphologic features were recorded according to Wortsman and have been confirmed: focal hyperechoic deposits of the distal ventral plate without involvement of the dorsal nail plate (may be subclinical and correlate with subungual keratosis), loss of definition of both nail plates adopting a wavy form, thickening of the nail bed, and an increased blood flow of the nail bed detected on PD sonography [99, 100]. Thickening of the nail, irregularities, and undulation of both plates have also been reported [101–103]. Stiffness of the nail plate, as determined by shear-wave elastography, is similar in affected and normal nails in psoriasis and in healthy controls [104].

Idolazzi et al. concluded that there are statistically significant differences between patients and healthy controls for the nail plate thickness which can be used as diagnostic criteria [103]. They proposed a cutoff of 0.63 mm for nail plate thickness to differentiate between psoriasis and healthy controls. Unfortunately, this cutoff has a sensitivity of only 70% and a specificity of 78% for discriminating patients from healthy controls. Not only using nail thickness to identify psoriasis is controversial because of the rather low sensitivity and specificity but also the proposed cutoff of 0.63 mm is under discussion: In another study, the mean thickness of the nail plate even in healthy controls exceeded the proposed cutoff of 0.63 mm [102]. Furthermore, not all studies could find a significant correlation with US nail thickness between psoriasis patients with and without nail involvement [105]. Sandobal et al. assessed the thickness of the nail *bed* of patients with nail psoriasis, psoriatic arthritis, rheumatoid arthritis and controls, and established a cutoff of 2 mm (80% sensitivity and 71% specificity) as a predictive factor for nail psoriasis and psoriatic arthritis [106], a cutoff which was confirmed by Vidat et al. [102].

Another potential future use for US in nail psoriasis may be to serve as an assessment tool for evaluating changes in time as alternative for clinical scoring systems, such as the NAPSI or the Nijmegen-Nail psoriasis Activity Index tooL (N-NAIL) [107, 108, 158]. Krajewska et al. have shown that US thickness of the nail plate, nail bed, and matrix increases with the mNAPSI [109]. However, abnormal nails on US do not correlate very well with clinical signs because US is very sensitive for subclinical nail anomalies. Clinical onychopathy was detected in only half of psoriatic arthritis patients with abnormal nails on US [105]. The predictive value of a psoriatic-type nail anomaly on ultrasonography with regard to the future occurrence of psoriatic arthritis is so far unknown. The specificity of nail abnormalities on US was investigated in patients with psoriatic arthritis, and one study compared psoriasis with rheumatoid arthritis and healthy controls [106, 110]. Patients with psoriatic arthritis and psoriasis showed a higher number of dysmorphic nails, also in majority of the clinical normal nails. When classifying those abnormalities, patients with psoriatic arthritis revealed loosening of the borders of the ventral plate, whereas patients with psoriasis showed focal hyperechoic involvement of the ventral plate without involvement of the dorsal plate, both different from controls and rheumatoid arthritis patients. Mean nail bed thickness and mean nail matrix thickness were slightly but statistically significantly increased in the psoriatic arthritis patients. These results indicate that US of nails has some specificity in psoriasis.

PD characteristics of nail psoriasis are less well defined than US characteristics. An increased blood flow of the nail bed is often reported as feature of nail psoriasis [99–101]. Although these and other PD changes of the nail have been reported, it must be realized that the nail bed is an extremely vascular site. This raises the question whether PD changes may necessarily reflect pathology. This question has been investigated in several studies with heterogeneous results. Aydin et al. reported PD signal covering >50% of the nail bed more frequently in healthy controls than in psoriasis patients with or without nail involvement [111]. The finding of less rather than more vascularity in the nail bed of psoriasis patients confirms the same finding from older studies measuring the resistive index [112] and using capillaroscopy [113]. Decreased blood supply in psoriatic nails may link to higher pressures in the nail bed or blood diversion to other sites of inflammation including enthesis and bone [111]. This altered blood diversion would also explain why for abnormal nails high PD signals of the nail bed may be less frequent in case of arthritis than in psoriasis [111], a finding which was not confirmed by others [102]. Not only the presence of arthritis has to be taken into account measuring the blood supply of the nail. Age is another factor because the maximal intensity of the Doppler signal has been shown to increase with age [105].

Microvascular changes in nail psoriasis have also been subject of a study comparing US and videocapillaroscopy findings in the nail fold [114]. The link between nail fold vessel resistive index measured by color Doppler US and capillary loops diameters measured using nail fold videocapillaroscopy was evaluated, and the morphological appearance of the nail bed in patients with psoriatic nail disease was compared with healthy controls. As discussed above, also in this study, patients with nail psoriasis had higher nail fold vessel resistive index in comparison with healthy controls. Tortuous capillaries in the proximal nail fold were detected in 62% of nail psoriasis patients and in 20% of healthy controls, confirming the other studies [101, 115]. The mean nail fold vessel resistive index was slightly higher in patients with nail psoriasis who had tortuous capillaries than patients who did not have tortuous capillaries. This had also been shown before by Marina et al. and by El-Ahmed et al. [101, 112].

Summarizing abovementioned microvascular studies, the blood flow not only in the nail bed but also in the nail fold is reduced in nail psoriasis. Decreased blood supply in the psoriatic nail bed was assumed to be caused by higher pressures in the nail bed or blood diversion to other sites of inflammation including enthesis and bone [111]. Decreased blood supply of the nail fold due to increased nail fold vessel resistance was explained by endothelial dysfunction and wall vessel thickening [101]. These microvascular changes in psoriatic nail disease have been shown repeatedly, but the significance and implications for disease diagnosis and follow-up are still unknown [100].

Ultrasound has also been investigated as a technique to distinguish between nail psoriasis and onychomycosis [116]. The main finding was a significantly higher PD signal at the nail bed and US of distal interphalangeal alterations in patients with nail psoriasis compared with those with onychomycosis. US measurement showed thinner nail plate and nail bed in psoriatic nails than in those with onychomycosis. The percentage of patients with a PD signal ≥2 at nail bed level was significantly higher in psoriatic onychopathy than in onychomycosis, and structural bone lesions were more frequent in psoriatic onychopathy than in onychomycosis. Because nail psoriasis is associated with changes of the distal interphalangeal joint, more changes related to arthritis are expected in psoriasis patients than in onychomycosis. No differences could be noticed between the extensor tendon and the presence of synovitis of the distal interphalangeal joint: Only 22.9% of patients with nail psoriasis showed synovitis in the distal interphalangeal joint on US [116]. However, psoriatic nails showed more frequently US structural damage in the distal interphalangeal joint (erosions, irregularities, or bone proliferation) than did nails with onychomycosis. These results suggest that the presence of structural

damage and higher PD signal are the main US findings supporting a diagnosis of psoriatic onychopathy.

Optical Coherence Tomography

Optical coherence tomography (OCT) is an optical analog of US using infrared light instead of acoustic waves. The reflection of the light waves from the tissue is measured and processed in order to improve the signal-to-noise ratio and transfer to a computer generating an OCT image [117]. This technique allows a more detailed assessment of the nail structure and vasculature than using ultrasound, dermoscopy, or videocapillaroscopy, but depth penetration is limited to 2 mm [117, 118].

OCT is able to show nail changes in nail psoriasis with prominent thickening in the ventral plate at the nail bed which is grossly inhomogeneous, "eroded," and irregularly fused with the underlying epidermis, which correlates with the clinical observation of subungual hyperkeratosis [117]. The deep nail bed also contains predominant black empty areas surrounding highly reflective tufts that resemble cotton balls or cloudlike structures. These nail bed findings are reported to be unique to psoriatic nails and are not seen in the healthy controls where the nail bed contains homogeneously reflective tissue with a linear superficial border proximal to the hyponychium [118]. The nail surface is rough and irregular with superficial fissuring. The white streaks within the nail plate correlate clinically as leukonychia and are seen predominantly in the mid-layer of the nail. Pitting is also clearly visualized as black ringed shapes that can be traced to a measurable depth using OCT. The resolution of OCT is higher than with US, but many patients have a normal OCT, while clinical findings are present, and some patients do not have clinical changes but an abnormal OCT [119]. The sensitivity of any OCT finding is only 44%, while the specificity is high with 96%.

Vascular features of OCT in nail psoriasis using dynamic OCT have been studied in psoriasis patients with nail changes and healthy control patients who underwent OCT imaging of the distal nail plate and proximal nail fold to quantify blood flow at depth [118]. Dilated vessels with a disorganized architecture in the psoriatic nails were depicted. Deep in the proximal nail fold, psoriatic nails had significantly increased blood flow and superficially dilated, disorganized blood vessels. Additionally, increased dynamic signal was diffusely seen deep to the proximal nail plate itself despite the increased nail thickness. The cross-sectional view showed a dense arrangement of blood vessels extending superficially.

Speckled variance OCT has been used in acrodermatitis continua of Hallopeau [120]. Speckled variance OCT showed a thickening, irregularity, and waving of the nail plate with some hyper-reflective spots; alteration of the nail bed with decreased reflectivity and increased vascularization; alteration of the proximal area, corresponding to the nail matrix, with thickening of the epidermal layer; and increased blood flow.

Recently, a scoring system for nail psoriasis severity based on OCT has been introduced [121]. Three scans are taken of each fingernail: a transverse scan from the lateral to the medial side and two longitudinal (proximal and distal) scans from the lunula to the distal nail. Leukonychia, pitting, diffuse surface waving, onycholysis, and subungual hyperkeratosis are scored as present or absent. Clinical and imaging nail outcomes were reported concordant in confirming improvement or worsening, while NAPSI was not always able to be responsive enough to pick up changes. Further studies with larger numbers and comparing OCT with other imaging tools and scoring systems are needed to validate its potential role as a nail biomarker.

In conclusion, OCT allows a more detailed assessment of the nail structure and vasculature than using US, dermoscopy, or videocapillaroscopy, but depth penetration is limited to 2 mm. A practical drawback to OCT is the rather steep learning curve in terms of maneuvering the device on nails. Operating the OCT device is user-dependent, and maintaining steady hands to reduce signal noise takes time.

Other Recent Diagnostic Developments

MicroRNA (miRNA) is a small noncoding RNA molecule that acts as posttranscriptional regulator that binds to complementary sequences in the 3′ untranslated regions (UTRs) of target mRNAs, resulting in silencing of their expression. This results in posttranscriptional regulation of gene expression. miRNAs are reported to play roles in the pathogenesis of diseases via effects on cell activities, such as migration, proliferation, immune response, or carcinogenesis. Dysregulation of serum miRNAs levels of miR-424 and miR-1266 and their potential role as a biomarker have been shown in psoriasis patients [122, 123]. The potential role of extracellular miRNAs as biomarkers for nail psoriasis has been evaluated recently [124]. Nail miR-4454 levels were significantly decreased in psoriasis patients with nail changes compared to those in patients with other diseases involving nail changes or healthy subjects. miR-4454 levels were not altered in psoriasis patients without nail changes, indicating that nail miR-4454 levels may serve as a useful biomarker for differentiating between psoriasis patients and patients with nail changes and patients with other diseases involving nail changes.

Nail Psoriasis as Predictor of Psoriatic Arthritis

One of the major conundrums in nail psoriasis is the relationship between skin, nail, and joint involvement. The relationship between these three localizations is especially important to establish the best treatment plan and to predict if an affected area can extend to another one worsening the prognosis. Psoriatic arthritis affects about 10–15% of patients with plaque psoriasis [125], with an incidence as high as 30% in dermatology clinics (where patients tend to have more extensive/severe psoriasis) [126]. About 70% of psoriatic arthritis patients have nail involvement, but minority of patients with nail psoriasis has or will develop psoriatic arthritis. Psoriatic arthritis often results in progressive structural joint damage and irreversible disability, even early in the disease course. Early identification and treatment of psoriatic arthritis may result in improved outcomes of arthritis and also nail disease since most treatments of psoriatic arthritis will also improve nail involvement. While it remains unclear which individual patients with psoriasis will develop psoriatic arthritis, several studies have identified potential risk factors for psoriatic arthritis among the group of psoriasis patients. Identified risk factors are more extensive skin disease and nail psoriasis [15, 127, 128]. The predicting value and true relevance of nail involvement as early indicator for psoriatic arthritis are under discussion because a higher incidence of psoriatic arthritis in nail psoriasis patients could not be confirmed in all studies [126]. Scarpa et al. suggested that distal interphalangeal joint involvement is always secondary to nail and distal phalanx involvement [129]. In the light of this hypothesis, it is essential to look at clinical and epidemiological data which may give insight in the development of psoriatic arthritis in nail psoriasis patients.

A population-based study demonstrated that 5.1% of psoriasis patients develop psoriatic arthritis over a 20-year period [127]. This study included 224 patients with nail involvement. In a multivariate analysis, the hazard risk was 2.24 to develop psoriatic arthritis in nail psoriasis patients compared to plaque psoriasis patients without nail involvement. So about 11% of nail psoriasis patients will develop psoriatic arthritis over a 20-year period, which means that 89% of nail psoriasis patients are still without joint involvement after 20 years. That most nail psoriasis patients will never develop psoriatic arthritis can also be simply concluded from other figures: Half of psoriasis patients have nail involvement, while psoriatic arthritis occurs in 10–15% of psoriasis patients in the course of the diseases, and not all of these psoriatic arthritis patients have nail involvement. Mathematically, this implies that less than 20–30% of nail psoriasis patients will *ever* develop joint involvement. Another study addressing nail psoriasis as a risk factor to develop psoriatic arthritis was designed as a pro-

spective cohort study involving psoriasis patients who did not have a diagnosis of arthritis at the time of study enrollment [128]. Data were obtained from 464 patients mostly recruited from dermatology clinics and phototherapy centers who were followed up for 8 years. A total of 51 patients (11.0%) developed psoriatic arthritis, 19.9% of patients with nail pitting, and 9.1% of the psoriasis patients without nail pitting (RR = 2.21). In univariate, but not in multivariate analysis, nail pitting was associated with a higher risk to develop psoriatic arthritis. Nail onycholysis was slightly more present in patients developing psoriatic arthritis, but not significantly.

According to the above discussed studies, the annual risk to develop psoriatic arthritis in psoriasis patients with nail involvement is 0.55–2.55%. In psoriasis patients without nail involvement, this risk is lower: 0.26–1.14%. So these studies show that psoriasis patients with nail involvement have a higher risk of developing psoriatic arthritis, although the absolute risk remains rather low. Looking at the results of those studies, some issues need to be addressed. One issue is the fact that both nail psoriasis and psoriatic arthritis are more frequently encountered in patients with severe psoriasis. This makes an overlap likely between nail and joint psoriasis and suggests rather an association (a relationship between the proposed risk factor and the disease exists) between nail psoriasis and psoriatic arthritis than a causation (the risk factor directly causes the disease). Also, disease duration may explain an association between nail psoriasis and psoriatic arthritis: Patients with a long history of psoriasis have a higher risk of developing nail disease as well as a higher risk of being confronted with psoriatic arthritis [15]. Another, and probably even more important, issue is the commonly used diagnostic criteria for the diagnosis of psoriatic arthritis, the CASPAR criteria [130]. According to these criteria, a patient must have inflammatory articular disease (joint, spine, or entheseal) with three other points from five categories. One of these categories is the presence of typical psoriatic nail dystrophy including onycholysis, pitting, and hyperkeratosis. So in patients with nail involvement, it is easier to make the diagnosis psoriatic arthritis than for similar psoriasis patients without nail involvement. In consequence, it is unavoidable that the diagnosis psoriatic arthritis will be made more often in patients with psoriatic nail disease than without.

In conclusion, the annual risk for psoriasis patients to develop psoriatic arthritis is limited. It is likely that psoriasis patients with nail involvement, in particular pitting, have a higher risk of developing psoriatic arthritis. There are reasons to assume that the association between nail psoriasis and developing psoriatic arthritis is, at least partly, caused by the fact that both are more frequently seen in patients with longer disease duration and with more severe psoriasis. Also, the diagnostic CASPAR criteria for psoriatic arthritis may lead to overestimation of the increased risk nail psoriasis patients have to develop psoriatic arthritis.

The Nail-Enthesitis Theory

Originally, it was thought that the link between arthritis and psoriasis could be explained by an autoimmune response to a common autoantigen in both skin and synovium [131]. In 2006, Scarpa et al. suggested that nail involvement is the main lesion in patients with psoriatic arthritis which pathogenically implies the involvement of the nail results in involvement of the distal phalanx and involvement of the distal phalanx results in involvement of the distal interphalangeal joint [129]. As a modification of this hypothesis, the nail-enthesitis theory was developed to explain a potential interaction between nail psoriasis and psoriatic arthritis of the distal interphalangeal joint. In this theory, not the nail is the main lesion anymore, but the entheses are suggested as disease epicenter [132]. Entheses are sites of insertion of tendons, ligaments, fascia, or capsules to bone; are anatomically, functionally, and physiologically associated with synovia; and form the "enthesis organ" or "synovio-entheseal complex." According to the nail-enthesitis theory, biomechanical stress or microtrauma at entheses in a genetically predisposed individual leads to enthesitis with production of cytokines, which

induce psoriatic nail changes, and enter synovial tissue, leading to arthritis [132, 133].

A fundamental assumption in the nail-enthesitis theory for the development of psoriatic arthritis is that the nail unit is rather a musculoskeletal appendage than a skin appendage. This assumption is partly based on MRI and histological studies which indicated that nails are functionally integrated with distal interphalangeal joint entheses [134–137]. Specifically, the extensor tendon, which is attached to the terminal phalanx, extends distally and is assumed to connect with the nail apparatus, making nail fascia an extension of the enthesis (Fig. 12.7). Therefore, according to the nail-enthesitis theory, it is possible that subclinical inflammation of the enthesis of extensor tendon, close to the nail matrix, could play a key role in nail pitting in psoriatic arthritis and psoriasis. Inflammation at the more distal collateral ligament anchorage of the nail, close to the nail bed, might play a role in onycholysis [134]. In particular in the field of rheumatologists, this theory has been adopted with enthusiasm. Some rheumatologists even consider nail psoriasis a manifestation of psoriatic arthritis [138], neglecting the fact that most nail psoriasis patients will never develop clinical signs of psoriatic arthritis and the lack of radiological correlation in distribution of distal interphalangeal joint arthritis between psoriatic arthritis patients with and without nail involvement [139]. The nail-enthesitis theory has been the fundament for numerous additional studies which can be divided into histological studies on the assumed anatomical relationship between the nail unit and the enthesis and clinical studies on the assumed

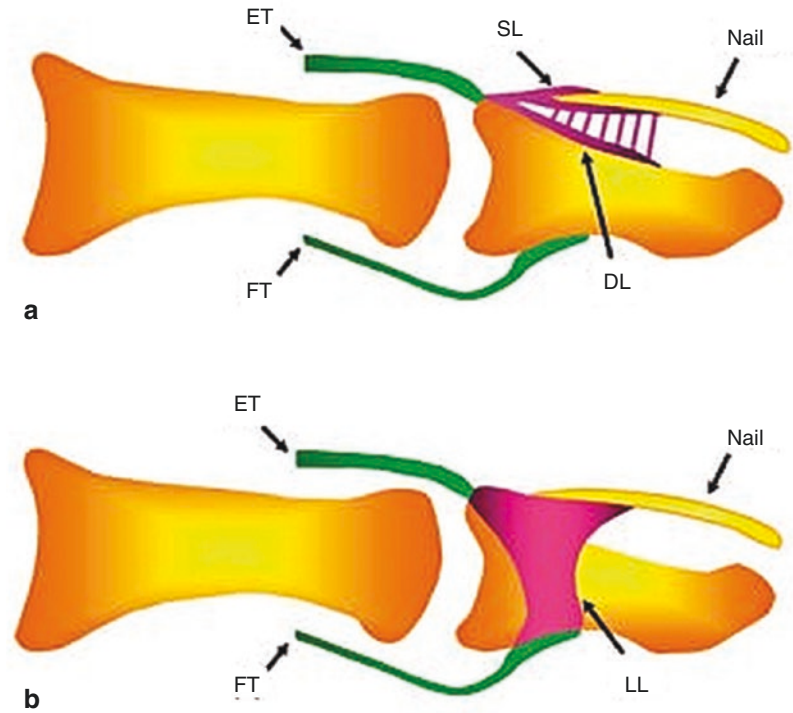

Fig. 12.7 Cartoon showing the link between nail, enthesis, and periosteum. (**a**) A midline sagittal section through the distal interphalangeal joint with fibers extending from the extensor tendon (ET) as superficial lamina (SL) on the dorsum of the distal interphalangeal joint. A further deep lamina (DL) also extends as fibers from the ET and forms a thick periosteum on the dorsum of the distal phalanx. Strands of fibers also link the nail plate to the periosteum. (**b**) A more lateral sagittal section of the distal interphalangeal joint with the lateral lamina (LL) attaching the side of the nail root to the flexor tendon (FT) demonstrating further anchorage of the nail by the entheses. (Republished with permission from McGonagle et al. [134] by Karger Publishers, Basel, Switzerland)

pathogenic interconnection between the nail unit, enthesis, and distal interphalangeal joint.

Studies on anatomical relationship between the nail unit and the enthesis have been summarized in detail by Perrin [140]. According to older histological and MRI studies, the ligaments and tendons of the distal interphalangeal joint are an integral part of the nail unit: The entire ligamentous structures of the base of the distal phalanx attach the nail unit to the distal interphalangeal joint (Fig. 12.7). This concept implies that the nail mesenchyme is completely derived from the periosteum and ligamentous structure of the distal phalanx. Recently, a study analyzing the elastic network of the nail mesenchyme demonstrated that the nail matrix mesenchyme is not the formerly assumed ligamentous connective tissue but a modified dermis [141]. This microscopic study was not able to show any connection between the extensor tendon and the nail apparatus. In a later study, it was histologically demonstrated that the previously assumed nail-embracing parts of the extensor tendon correspond to three different microanatomical structures: the nail dermis and its fibrous root, the subcutaneous proximal nail fold, and the periosteum [140]. These results are not in agreement with older studies [134, 135], but this study did look at more levels of the nail apparatus and used elastic stain and not only trichrome or H&E stains. This different approach allowed a more detailed analysis of the various connective tissue structures of the base of the distal phalanx. Based on these findings, the nail-enthesitis theory relies on an oversimplified anatomy because there is no direct connection between the nail unit and the extensor tendon [140].

Several clinical studies report findings which also have shed new light on the relationship between nail psoriasis, enthesitis, and distal interphalangeal joint arthritis. Radiological studies on enthesitis in nail psoriasis patients showed a high percentage of systemic enthesitis of the knee, heel, or elbow in nail psoriasis patients [142] or demonstrated that nail dystrophy is more common and severe in psoriatic arthritis *patients* with distal interphalangeal involvement than those without, without reporting if the nail dystrophy was located in the same *digit* as the distal interphalangeal involvement [14, 143, 144]. From these studies, it can be concluded that enthesitis is more frequent in patients suffering from nail psoriasis, but this enthesitis can be at a site distant from the nail. These studies do not support the nail-enthesitis theory which assumes a direct anatomical and pathogenic relationship between nail psoriasis, enthesitis, and distal interphalangeal joint arthritis: All these three should be present in the same digit at the same time, but digits with nail psoriasis, enthesitis, and distal interphalangeal joint arthritis at the same time appear to be exceptional. Two radiographical studies reported higher severity of nail psoriasis with adjacent clinical (but not radiological) distal interphalangeal joint arthritis than without adjacent distal interphalangeal joint arthritis, suggestive for a relationship between nail and distal interphalangeal joint [138, 145]. However, this was not a *conditio sine qua non* because severe psoriatic arthritis could also occur without any signs of nail psoriasis [138]. Enthesitis, the proclaimed epicenter of both nail psoriasis and psoriatic arthritis was only present in a small number (16%) of patients with nail involvement, and a relationship between enthesitis and nail involvement of the same digit was not reported.

Distal interphalangeal joint damage can be detected earlier and more precise by ultrasonography than with radiography, especially if performed in the early morning. In US studies in early psoriatic arthritis patients, the lesion most frequently reported is enthesitis (enthesial thickening) followed by synovitis. Studies focusing on enthesial thickening of the extensor tendon in nail psoriasis reported more enthesial thickening in psoriatic arthritis digits with nail involvement compared to psoriatic arthritis digits without nail involvement [146–148]. The findings of these studies support the nail-enthesitis theory, but several other studies point toward another direction: The link between enthesopathy on US and clinical nail disease was not confined to matrix psoriasis (pitting) but was also seen with onycholysis (nail bed psoriasis) which therefore would not be expected to be related to extensor tendon disease

[147]. Furthermore, synovitis at distal interphalangeal level was not associated with clinical nail involvement neither in psoriatic arthritis nor in plaque psoriasis patients [146, 149]. Subclinical extensor enthesitis has been noted not only in adjacent nails with signs of psoriasis but as often in normal adjacent nails [146, 150].

Other studies also show results which cannot be explained by the nail-enthesitis theory. A comparison of onychomycosis patients and nail psoriasis patients did not show differences in thickness of the extensor tendon entheses and joints in these two nail disorders [116]. Acosta-Felquer et al. demonstrated that the nail, the enthesis, and the distal interphalangeal joint are not the only three structures that are involved in nail psoriasis and psoriatic arthritis. Clinical nail disease was linked not only to enthesial thickening but also to both epidermal thickening and dermal edema [146], suggesting that nail psoriasis cannot only be linked to an inflammatory reaction of the enthesis but also to inflammation of all tissues in the vicinity of the nail unit. This inflammation beyond anatomical borders may be explained by the cytokine overflow theory, which assumes that cytokines produced from the nail units overflow to the nail fold and small joints and can induce nail fold psoriasis and psoriatic arthritis [151].

Summarizing the above discussed studies and putting them into perspective, it can be concluded that:

- Enthesopathy can be detected more often in nail psoriasis patients than in psoriasis patients without nail involvement. The entheses of the extensor tendons may be more often involved if the nail of that digit is affected by nail psoriasis, but also the entheses of remote joints, like the knee, heel, or elbow, are more often involved in nail psoriasis patients [14, 138, 142–148].
- Enthesopathy can also be found in many psoriasis patients with clinically normal nails [146].
- In nail psoriasis, not only the enthesis may show signs of inflammation, but also dermis and epidermis of the periungual skin are frequently abnormal [146].
- Local distal interphalangeal joint synovitis might *not* occur more often than remote distal interphalangeal joints synovitis in nail psoriasis patients [146, 150].
- US signs of synovitis are not typical for nail psoriasis but can also be found in onychomycosis patients who are not prone to develop arthritis [116].

All these results suggest that the same predisposition is needed for the development of nail psoriasis and for the development of enthesitis, but an anatomical relationship is questionable. The nail-enthesitis theory assumed direct anatomical relationship between nail, enthesis, and distal interphalangeal joint. The major virtue of the nail-enthesitis theory is its simplicity. However, clinical and anatomical studies frequently failed to provide data supporting the model, and therefore, it is not unlikely the scientific interest in the nail-enthesitis theory will gradually fade away.

The Psoriatic Nail Plate and Transungual Delivery of Drugs

In order to understand the degradation mechanism induced by psoriasis in fingernails, the chemical structure and elemental composition of fingernail keratin, as well as the surface morphology of healthy and psoriatic fingernails, were compared [152]. A lower content of disulfate bridges and conformation changes of the keratin were found in psoriatic fingernails, resulting in weaker adherence of the onychocytes, inducing changes in surface morphology in terms of uniformity, density, and roughness.

The consequence of microstructural alterations in the psoriatic nail regarding delivery of topical drugs has also been studied [153]. The hard structure of a healthy nail plate, made up of hard keratins stabilized by disulfide bridges, results in a compact structure across which drug molecules diffuse with difficulty. In vitro permeation (diffusion) studies showed that psoriatic nails, with increased porosity and numerous pores and cracks, seemed more permeable to clobetasol than healthy nails. However, the differ-

ences were not significant. Cutrin Gomez et al. are modest in their conclusion: They argue that possible increased permeability of a psoriatic nail plate makes it likely that potential effective formulations by transungual delivery of the compound may be effective at initial stages of a treatment for psoriatic nails. After some recovering of the nail, the treatment will fail because improvement of the nail plate will block the further permeation through the nail plate. However, since the nail plate is synthesized in the matrix and not below the nail plate, this modesty is unnecessary. Moreover, the fact that these, and most, permeation tests use prehydrated nails is another issue that has produced an unclear exploration of the effects of treatments.

Watery compounds appear to be a more important issue because water increases porosity and swelling, alters impedance on the nail structure, and is considered a penetration enhancer itself [153]. An attempt to overcome these practical issues concerning transungual delivery of drugs is the use of a fractional ablative laser to make holes in the nail plate [154]. Laser ablation was found to affect the mechanical properties of a hoof membrane (an in vitro model of the human nail). In this in vitro permeation study, laser ablation resulted in a significant increase in drug cumulative delivery, flux, and permeability coefficient.

Treatment of Nail Psoriasis

Effective management of nail psoriasis is often complex and challenging even for the most experienced clinician. A successful therapeutic approach should include general advices for all patients with nail psoriasis (Table 12.1) and an individualized choice from all available pharmacological treatments (Table 12.2). Onychomycosis, especially of the toenails, has been demonstrated to be more common in patients with psoriasis and could koebnerize psoriatic nail disease. When suspected, onychomycosis should be diagnosed by direct microscopy, culture, or biopsy, and antifungal treatment should be prescribed along with nail psoriasis treatment [155].

Table 12.1 General advices for all patients with nail psoriasis [155]

Avoid biting, tearing, and traumatizing the nails; tangential filing; frequently applying and removing nail cosmetics; frequent water contact; artificial or gel nails; pulling, biting, and cutting cuticles; wearing high heels or narrow-toed shoes; and cutting toenails round at the edges.
Wear heavy-duty cotton gloves for dry work and light cotton gloves underneath vinyl gloves for wet work.
Keep nails short in nail bed psoriasis.
Frequently use hydrating topical products on hands and nails.
An orthopedist or podiatrist should be consulted for the fitting of proper shoes and shoe inserts if anatomical problems, such as bunions, improper foot strike, pronators, or supinators, are present.

An optimal effect of any treatment may take up to 1 year. Accepted treatment modalities include topical agents, intralesional injections, conventional systemic medications, small molecules, and biologic agents. The role of non-pharmacological treatment options, including phototherapy, photodynamic therapy, radiotherapy, and laser therapy, is limited [3]. In this section, recent publications on treatment of nail psoriasis will be discussed. Comprehensive reviews of older publications are available [3, 4, 58].

One of the most important recent publications on nail psoriasis is a consensus paper which discusses recommendations for the definition, the evaluation, and the treatment of nail psoriasis in adult patients with no or mild skin psoriasis [155]. The authors emphasize that it is difficult to balance studies on nail psoriasis because most of the available intervention studies were not designed to specifically address nail psoriasis. Study results often refer to subpopulations with nail disease, among larger populations with cutaneous psoriasis, arthritis, or both. A summary of the treatment recommendations of this consensus group of nail psoriasis experts can be found in Fig. 12.8. In summary, in few-nail disease ($\leq$3 nails involved), intralesional steroid injections were considered the treatment of choice in the case of matrix involvement only. The second-line treatment should be topical steroids, topical vitamin D analogs, topical vitamin D analogs in

Table 12.2 Available treatments for nail psoriasis

Topical
Steroids
Vitamin D derivates (calcipotriol, calcitriol, tacalcitol)
5-Fluorouracil
Calcineurin inhibitors (tacrolimus, ciclosporin)
Retinoids (tazarotene)
Combination of topical corticosteroid and calcipotriol
Combination of topical corticosteroid and tacalcitol
Indigo naturalis oil
Intralesional
Steroids
Methotrexate
Ciclosporin
Conventional systemic
Methotrexate
Ciclosporin
Retinoids
Fumaric acid
Small molecules
Apremilast
Tofacitinib
Biologics
Adalimumab
Briakinumab
Brodalumab
Certolizumab pegol
Etanercept
Golimumab
Guselkumab
Infliximab
Ixekizumab
Risankizumab
Secukinumab
Ustekinumab
Other
PUVA
UVB (narrow band, excimer)
Grenz rays
Electron beam therapy
Superficial radiotherapy
Brachytherapy
Laser therapy (pulsed dye laser (595 nm), Nd:YAG laser (1064 nm))

combination with topical steroids, topical retinoids, topical keratolytic agents (e.g., urea nail lacquer, salicylic acid), or topical 0.1% tacrolimus. Topical steroids alone or in combination with topical vitamin D analogs were suggested as first-line treatment for nail psoriasis limited to the nail bed in few-nail disease. The steroids could be used under occlusion, both for matrix and bed disease, but occlusive treatment is recommended not to exceed 1 month due to possible local side effects. If both nail bed and nail matrix are involved in few-nail disease, the first-line treatments of choice are intralesional steroid injections and/or topical steroids in combination with topical vitamin D analogs. Alternative treatments in these patients are topical vitamin D analogs, topical steroids, topical retinoids, or topical 0.1% tacrolimus. If more than three nails are involved, the treatment of choice largely should depend on the discussion between the clinician and the patient in which the severity of nail involvement, the impact on QoL, and patient's preferences all are included. Both topical and systemic treatments are options in these patients. According to this consensus paper, acitretin, methotrexate, ciclosporin, small molecules, and biologics may be employed for the systemic treatment of nail psoriasis. Acitretin should be initiated at 0.2–0.4 mg/kg for 6 months or until at least a moderate improvement is documented. Ciclosporin is only recommended for short-term treatment in doses of 3–5 mg/kg. Methotrexate can be employed in doses up to 15 mg/week and also as maintenance treatment. The nail expert group concluded that TNF-α inhibitors infliximab, etanercept, adalimumab, and golimumab; IL-12/IL-23 inhibitor ustekinumab; IL-17 inhibitors secukinumab and ixekizumab; phosphodiesterase 4 inhibitor apremilast; and Janus kinase (JAK) 1/3 inhibitor tofacitinib could be considered for systemic treatment of nail psoriasis. In patients treated for psoriatic arthritis or plaque psoriasis, the pegylated TNF-α inhibitor certolizumab pegol and the IL-23 inhibitor guselkumab appear to have a positive effect on nail psoriasis [155]. Treatment with these agents results in rapid and significant improvement of nail psoriasis when used in patients with nail psoriasis and cutaneous disease, arthritis, or both.

Another consensus paper on treatment of nail psoriasis was developed by the Medical Board of the National Psoriasis Foundation and additionally defined scenarios for nail psoriasis patients with significant skin disease [156]: For patients with significant skin and nail dis-

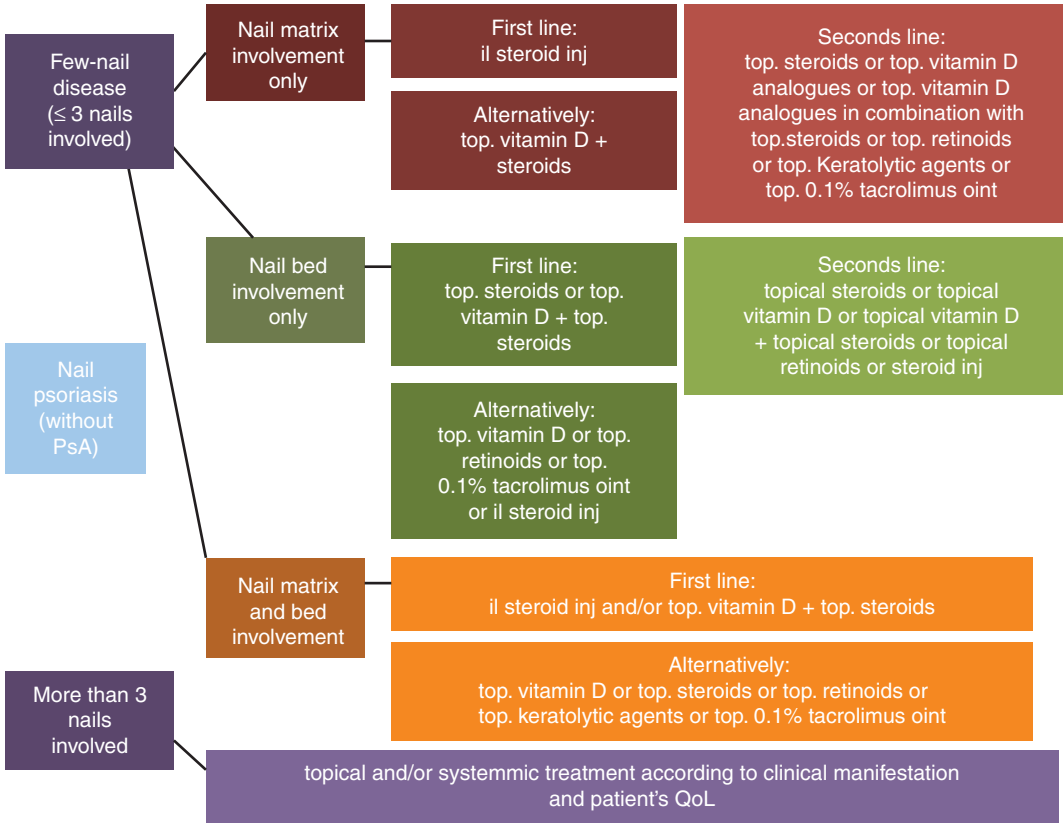

Fig. 12.8 A summary of the treatment recommendations of a consensus group of nail psoriasis experts [155]. Clinical treatment algorithm for nail psoriasis according to the number of nails involved and the location of the psoriatic lesion. il, intralesional; inj, injection; oint, ointment; psoriatic arthritis, psoriatic arthritis; QoL, quality of life; top, topical. (Republished with permission of Elsevier [155])

ease, adalimumab, etanercept, and ustekinumab were strongly recommended, and methotrexate, acitretin, infliximab, and apremilast were recommended. Finally, for a patient with significant nail, skin, and joint disease, adalimumab, etanercept, ustekinumab, infliximab, methotrexate, apremilast, and golimumab were recommended.

Treatment of Nail Psoriasis: Limitations of Clinical Studies

It is hard, or even impossible, to compare results from studies because of heterogeneity in the type and reporting of nail psoriasis outcome instruments [157]. The first limitation in comparing studies on the treatment of nail psoriasis is based on inclusion of patients. Most studies primarily focus on plaque psoriasis or on psoriatic arthritis in which nail data are secondary endpoints. Many of these studies struggle with the definition of nail psoriasis. In some studies, patients were considered to have nail psoriasis who had at least one single psoriatic nail feature, such as a single or more pits, leukonychia, red spot lunula, crumbling, Beau's lines, onycholysis, subungual hyperkeratosis, splinter hemorrhages, and oil-drop sign [40]. Using this liberal definition of nail psoriasis results in high percentage of included patients in plaque psoriasis studies but has consequences for the results: A patient included because of a single pit will have complete cure if this single pits disappeared after some time.

The most used nail psoriasis outcome instrument is the NAPSI [158]. However, the NAPSI

often is considered suboptimal for evaluating therapy responses in nail psoriasis. For example, significant and meaningful clinical improvement in the severity of nail psoriasis is sometimes not reflected in the NAPSI score [159]. Furthermore, the NAPSI has an interobserver reliability regarding total NAPSI score which is good, but target NAPSI score shows only moderate agreement [160]. The NAPSI system also contains several assessing parameters, such as leukonychia and red spots in the lunula, which are not significantly related to severity of the disease. On the other hand, the NAPSI does not consider factors which are relevant for patient's experience of severity, such as the number of pits per quadrant, the size of an oil spot, or the thickness of subungual hyperkeratosis. Because of all these restrictions, an appropriate nail psoriasis scoring system that correlates well with clinical severity is required [40]. Of all scoring system for nail psoriasis, the validated N-NAIL appears to correlate best with clinical severity as determined by physician global assessment (PGA) [161] and has a better responsiveness than the NAPSI [162].

Cosmetic Treatments

Many nail psoriasis patients suffer from pain, but visibility of the abnormal nails also has major social impact. Cosmetic treatments for nail disease will not influence the pathogenic process that results in formation of abnormal nails but may be important for many patients because it decreases the social impact. In general, patients can attempt to disguise unsightly psoriatic nails by using nail polish (lacquer, enamel), but frequently applying and removing nail cosmetics is not advised. Nail enhancements such as acrylic nails are not advised. Penetration of active concentrations of drugs from a nail lacquer through the nail plate to the nail bed is still rather unlikely. Therefore, even nail lacquers containing active antipsoriatic drugs cannot be advised.

Several primarily cosmetic treatments have been investigated in nail psoriasis. K101-03, a marketed topical treatment containing propylene glycol, glycerol, urea, and lactic acid, was investigated if it could produce cosmetic improvements in affected nails [163]. During and after treatment, patients rated the overall appearance of their nail. At 8 weeks, 94% of patients reported at least some improvement, while 15% reported very good improvement.

Topical Treatments

Topical treatments used to be the mainstay therapies in nail psoriasis. Gradually, the focus in clinical research has shifted toward systemic treatment, in particular toward small molecules and biologics. However, it is reasonable to assume that in daily clinical practice, many more patients with uncomplicated nail psoriasis are treated topically than with systemic therapies. The past couple of years, only few new data became available from studies of topical therapies in nail psoriasis. Topical application of clobetasol propionate 0.05% solution applied once daily for 4–6 months on the periungual tissues and nail bed was studied in mild nail psoriasis [164]. Ten out of 15 patients showed at least a marked improvement of the nail lesions, and five achieved complete resolution. Improvement was noted on nail matrix signs of nail psoriasis but more on nail bed signs, similar to the results in the clobetasol cream study [165]. The fact that only eight of the patients completed the study may be an indication that the solution does not contribute very much to patient compliance and satisfaction.

Iontophoresis is a technique that can be used to facilitate drug penetration. Triamcinolone acetonide iontophoresis (TI) has been compared with topical calcipotriol/betamethasone dipropionate [166]. Patients received six monthly TI treatment sessions on one hand and daily application of topical calcipotriol/betamethasone dipropionate on their other hand. The results did not show any difference between the therapeutic effects of TI and topical calcipotriol/betamethasone dipropionate regarding the nail bed score, matrix score, and total NAPSI.

Indigo naturalis (Qing Dai) is a plant extract widely used in traditional Chinese medicine. It

has been propagated as a topical treatment for nail psoriasis [167]. Several clinical trials showed interesting results, but in the past years, no new information became available on the position and availability of Lindioil®, an oil containing indigo naturalis extract for treatment of nail psoriasis.

Intralesional Treatments

Intralesional therapy in nail disorders has several advantages above topical or systemic treatments [168]. It is able to treat unreachable parts of the nail unit as noninvasively as possible, avoids barriers in the way of drug penetration resulting in effective levels of drugs at the site of action, and may establish a tissue depot for a prolonged release of drugs. Locally injected steroids have a long history in the treatment of nail psoriasis, and their efficacy is beyond dispute. The existing evidence suggests that intralesional injection into the nail bed and matrix are particularly effective for alleviating lesions caused by psoriasis of the nail matrix and also has moderate effects on nail bed signs. Nail bed injections are extremely painful without anesthesia, while nail matrix injections are bearable for many patients. A randomized comparison of efficacy and safety of intralesional triamcinolone injection, clobetasol propionate ointment, and placebo for psoriatic nails has been published recently [169]. Triamcinolone (10 mg/mL, 0.02–0.1 mL) was given every 2 months intradermally by using De Berker's technique [170]. Clobetasol propionate (0.05%) ointment was applied at the proximal nail fold and at the hyponychium of the target nail twice daily, without occlusion, for a 6-month period. Initially, intralesional corticosteroids were more effective than topical applied corticosteroids. However, at the 6-month visit, no longer any statistically significant difference was found between the groups. Therefore, intralesional therapy with triamcinolone should be considered an effective, but temporary treatment of nail psoriasis.

Intralesional treatment of nail psoriasis is a safe therapy but not without risk of complications or side effects. Side effects after intralesional corticosteroids are well known [3]: short-term paresthesia and focal pain that may last for several months, hematoma formation is rather common, and loss of the nail plate. Occasionally, nail fold atrophy can be encountered, which is often reversible. Chronic topical therapy can lead to complications of the "disappearing digit" with atrophy of the underlying phalanx. Rupture of the extensor tendon has also been reported after local injection of steroids. Recently, the Nicolau syndrome (embolia cutis medicamentosa) was reported following intramatrical triamcinolone injection [171]. The Nicolau syndrome cutis is a rare complication following parenteral administration of any drug and is characterized by severe painful local necrosis at the site of injection, eventually healing with scarring. The reported patient presented with pain, redness, and swelling of a toe after an intramatrical injection to the nail. Eventually, the toe symptoms completely resolved.

As an orally or subcutaneously administered systemic compound, methotrexate is one of the most used systemic treatments in plaque psoriasis, psoriatic arthritis, and nail psoriasis. Apart from systemic administration, the drug has started a new career as an intralesional treatment in nail psoriasis. Intralesional treatment of methotrexate appears a potential interesting intralesional therapy as it provides a higher concentration of the drug at the site of action while avoiding the complications seen with triamcinolone acetonide which are discussed in the previous section. The first case report on intralesional methotrexate was in 2011 [172]. In 2017, Grover et al. reported four patients with very mild nail psoriasis in which about 50% improvement in NAPSI was measured at 15 weeks [173]. Patients were treated with an injection of methotrexate (0.1 mL of a 25 mg/mL solution) into the nail bed. An insulin syringe with 30G needle was introduced into the proximal nail fold at a tangential plane and advanced to the nail bed until loss of resistance was felt. The solution was then infiltrated into the nail bed until blanching of the nail bed occurred. The needle was then slowly withdrawn and pressure applied for hemostasis. Patients were offered the choice of receiving injections under digital

anesthesia. Five such treatment sessions were given, with 3-week intervals between each session. Thereafter, the dosing intervals were increased to 4–6 weeks, and patients were followed up for further 3–6 months. Reported adverse effects were pain, injection site pigmentation, and nail bed hemorrhage.

Intralesional methotrexate has not only been used in the nail bed but also in the nail matrix [174]. Mittal and Mahajan compared intramatrical injections methotrexate (25 mg/mL), cyclosporine (50 mg/mL), and triamcinolone acetonide (10 mg/mL). A volume of 0.05 mL was injected from each lateral angle of the proximal nail fold, forming a "V." Each nail was given two injections with a 6-week interval and graded at 24 weeks using the NAPSI. In both methotrexate and triamcinolone acetonide groups, half of the nails showed >75% improvement. In the cyclosporine group, less often improvement was seen. However, differences between the three treatments were not statistically significant. This study has been criticized by others [175]. Their main concern is the fact that the formulations of antipsoriatic agents injected intramatrically in this study are not depot agents. They raise the question if the action of these drugs can last up to 24 weeks because the elimination half-life of methotrexate and cyclosporin is only hours. Improvement in nail psoriasis might be caused by the reverse Koebner phenomenon, which is defined as the disappearance of a dermatosis at the site of injury. Another issue is the optimal dose of methotrexate that should be injected. While in the study of Mittal and Mahajan and another case report [176] 25 mg/mL was used, another successful intramatrical methotrexate treatment was reported in a patient that was treated with an injection of methotrexate 0.1 mL of a 5 mg/2 mL solution [177].

Systemic Treatments

Methotrexate

Several studies have shown efficacy of systemic methotrexate as a slow-acting but effective drug in nail psoriasis [3]. A comparison with briakinumab showed less improvement in patients on methotrexate than on the anti-IL-12/anti-IL-23 monoclonal antibody, but the design of the study was not in favor of methotrexate [178]. Recent studies on oral treatment with methotrexate are sparse, but very interesting data on efficacy of methotrexate in nail psoriasis can be distilled from the METOP trial [179]. Methotrexate reduced the activity of nail psoriasis within 16 weeks as measured by the target NAPSI score (−22%) of the worst fingernail, whereas placebo had no effect. After 52 weeks of methotrexate treatment, eight (14%) of 59 patients showed complete clearance of the target nail, while the mean target NAPSI improved moderately (−46%). Follow-up of nail psoriasis was also included in an open-label study in psoriatic arthritis patients with mild nail involvement, with a mean mNAPSI score of 8 [180]. After 12 weeks of treatment, the mean change in mNAPSI was −2, so 25% mNAPSI improvement.

The Swiss Dermatology Network for Targeted Therapies has analyzed data of 66 patients with moderate-to-severe psoriasis who participated in their registry [181]. At 12 weeks, nail psoriasis improved from a mean NAPSI of 16.4 to 13.0 (−18%), which did not reach significance at this very early time point.

Small Molecules

Apremilast

Efficacy of the oral PDE-4 inhibitor apremilast on nail psoriasis has been suggested by case reports [182] but was also a secondary endpoint in the ESTEEM 1 and ESTEEM 2 studies [183–185]. In these studies, patients were randomized to apremilast 30 mg twice daily or to placebo. Both studies showed improvement in nail psoriasis: At week 16, apremilast produced 22.5% improvement in NAPSI (placebo +6.5%) in the ESTEEM 1 study and 29.0% improvement (placebo −7.1%) in the ESTEEM 2 study. At week 32, apremilast produced 43.6% improvement in NAPSI in the ESTEEM 1 study and 60.0% improvement in the ESTEEM 2 study. Both nail bed and nail matrix psoriasis improved. A NAPSI-50 response was seen in 33.3% (ESTEEM

1) and 44.6% (ESTEEM 2). The NAPSI improvements were sustained over time until week 52 (60% NAPSI improvement) but only in PASI responders. Among these PASI responders, NAPSI-50 achievement in ESTEEM 1 and ESTEEM 2 was 63–69% at week 52.

The LIBERATE trial evaluated long-term efficacy and safety of apremilast in biologic-naive patients with moderate-to-severe plaque psoriasis [186]. Patients were treated with apremilast 30 mg twice daily during 104 weeks. Mean percentage change from baseline in target NAPSI was −42.8% at week 52 and − 48.2% at week 104. At week 104, target NAPSI-50 was achieved by 60.4% of patients. The UNVEIL trial also had data on nail psoriasis in patients on apremilast for 52 weeks [187, 188]. The trial differed from the ESTEEM 1 and 2 trials as its patients had milder baseline skin disease, and patients were required to be naive from systemic and biologic treatments. At 16 weeks, apremilast was not more effective than placebo regarding reduction of the target NAPSI. Mean target NAPSI improvement at week 52 was 50%. Sixty-three percent of patients achieved a NAPSI-50 response at week 52.

In a phase IIb apremilast study in palmoplantar psoriasis, the PSOR-005 study, patients receiving 30 mg of apremilast and 10 mg of apremilast achieved a significantly higher reduction in NAPSI from baseline compared to placebo (42.9% vs. 33.3% vs. 0%) at week 16 [189]. NAPSI-50 was achieved by 45.5% in the apremilast 30 mg group, 31.5% in the apremilast 10 mg group, and 18.2% in the placebo group.

Another approach for delivering apremilast to the nail unit was followed by Kushwaha et al. [190]. A nail lacquer formulation containing apremilast was prepared which was found to be capable of delivering a substantial amount into the nail apparatus in vitro. This mode of drug delivery was presented as a potential option for the treatment of nail psoriasis, but limitations of the in vitro studies on permeation of drugs through a nail are well known and discussed in the section "The psoriatic nail plate and transungual delivery of drugs."

Results from the ESTEEM, PSOR-005, and LIBERATE trials suggest that oral apremilast is a rather slow acting but effective compound in treating nail psoriasis which is not superior to biologics. However, inclusion criteria and outcome measures are very different between studies with apremilast and with biologics. Therefore, it is hard to conclude that apremilast has worse efficacy as biologics in treating nail psoriasis.

Tofacitinib

Tofacitinib is an oral JAK 1/3 inhibitor which blocks signaling of key cytokines implicated in the immune response and inflammatory pathways. It reached the market for rheumatoid arthritis and is also approved for treating psoriatic arthritis and ulcerative colitis. In dermatology, off-label use is being reported to be of benefit for patients with psoriasis, alopecia areata, atopic dermatitis, and vitiligo. Positive experiences in cases of refractory psoriatic nail dystrophy have been reported [191, 192], and results of the OPT Pivotal studies are also available [193]. Across the OPT Pivotal 1 and OPT Pivotal 2 randomized controlled studies in plaque psoriasis patients, 408 patients with nail involvement received tofacitinib 5 mg, 404 received tofacitinib 10 mg, and 206 received placebo. In OPT Pivotal 1, at week 16, the mean percentage change from baseline in NAPSI score was −14.2% (tofacitinib 5 mg BID), −41.5% (tofacitinib 10 mg BID), and + 55.6% (placebo). Also, OPT Pivotal 2 showed differences between tofacitinib and placebo: The mean percentage change from baseline in NAPSI score was −21.6% (tofacitinib 5 mg BID), −26.0% (tofacitinib 10 mg BID), and +15.8% (placebo). In the latter study, only the higher-dose tofacitinib was significantly better than placebo in reducing the NAPSI.

A post hoc analysis of the same patients with existing nail psoriasis assessed the NAPSI score and proportions of patients achieving at least 50% reduction in NAPSI from baseline (NAPSI-50), NAPSI-75, or NAPSI-100 [194]. At week 16, significantly more patients receiving tofacitinib 5 mg and tofacitinib 10 mg versus pla-

cebo twice daily achieved NAPSI-50 (32.8%, 44.2% vs. 12.0%), NAPSI-75 (16.9%, 28.1% vs. 6.8%), and NAPSI-100 (10.3%, 18.2% vs. 5.1%), respectively. At week 52, the number of patients achieving a NAPSI-50 was similar to that at week 16, which is different from most studies with biologics in which relevant further improvement can be seen after week 16. Limitations of the study were the doubtful design with re-randomization of placebo patients to tofacitinib at week 16 and the discontinuation of clinical nonresponders at week 28. The latter makes it impossible to compare results with other studies. Both matrix signs of nail psoriasis (pitting) and nail bed signs (onycholysis, subungual hyperkeratosis) showed improvement. Improvement was somewhat better in patients without psoriatic arthritis. These results suggest that the JAK might be a therapeutic target for the nail psoriasis patient population, although results with tofacitinib in these patients indicate less efficacy than many of the biologics.

Biologics

Biologics are monoclonal antibodies interfering in several focused pathogenic steps of the assumed pathogenesis of psoriasis, thus reducing the clinical features. In this pathogenic cascade, various cells and mediators have been identified or are postulated to play a role, including keratinocytes, dendritic cells, T lymphocytes, complement proteins, and many cytokines and chemokines. Biologics interfering in several pathogenic steps prevent the expression of the full pathogenic cascade, thus reducing the clinical features. Biological therapies may be considered the fastest and most effective treatments for nail psoriasis [3]. With all for psoriasis-approved biologics, clinical improvement may be noticed already after 8 weeks [195]. Adalimumab, infliximab, ustekinumab, and etanercept seem to have comparable effectiveness in reducing signs of nail psoriasis according to a retrospective study [195, 196]. Since then, new powerful biologics have been introduced, and comparative studies are rare. Not only new biologics but also new data on established biologics will be discussed in the next sections.

Adalimumab

The anti-TNF antibody adalimumab is the only biologic which is FDA approved for treatment of nail psoriasis. It has been studied extensively for this indication, and treatment with adalimumab mostly results in relevant improvement of nail psoriasis. Several older studies have been summarized in 2016 [3]. Newer studies confirm efficacy of adalimumab in treatment of nail psoriasis.

The BELIEVE study already had shown efficacy of adalimumab on nail psoriasis as a secondary endpoint in a post hoc analysis of this randomized controlled trial (RCT) in psoriasis patients [197]. Results of the first RCT evaluating improvement of nail psoriasis as primary endpoint were published in 2018 and 2019 [198, 199]. At 26 weeks of adalimumab treatment, 47.4% achieved a 75% improvement in modified NAPSI, increasing to 54.5% at week 52. Complete clearance was achieved in 6.6% at week 26, which increased 17.9% at week 52. Similar results were seen with the rate of achievement of fingernail PGA 0/1 with ≥2 grades of improvement from baseline.

In an observational prospective postmarketing study, the effectiveness of adalimumab in the treatment of nail psoriasis in routine dermatologic practice was evaluated in 157 patients [200]. Eighty-four percent of the patients achieved a good clinical response upon treatment with adalimumab: The mean percentage change in the NAPSI score was −81.6%. Complete clearing of the nails (i.e., a NAPSI score of 0) was achieved by 40.0% of patients at 12 months. There was also a marked improvement in QoL: The mean DLQI showed an improvement of 88% (from 10.2 to 2.2) during 12 months of treatment.

Switching from one biological agent to another may prove effective even when response to the first one is inadequate. This is the result of a study by Sator et al. who evaluated the effectiveness, safety, and QoL outcomes in patients with plaque psoriasis who had switched to adalimumab from efalizumab, infliximab, or etanercept [201]. Some of participating patients had an

unsatisfactory response to prior biologic agents, but the vast majority had initially achieved a satisfactory response but lost it over time or discontinued treatment due to intolerance/side effect(s) or other reasons (e.g., restart after regular stop of etanercept). The mean percentage of improvement after 1 year of adalimumab in the 34 patients suffering from nail involvement was reported to be 83.6% for NAPSI. Summarizing recent and older data on adalimumab in nail psoriasis, this biologic is a powerful drug to treat nail psoriasis, and its efficacy can be proven by a solid number of studies.

Brodalumab

Brodalumab is a monoclonal antibody that targets and blocks the signaling pathway of interleukin receptors (IL-17A, IL-17F, and IL-23), which has been proven effective for psoriasis treatment. No full publication has appeared in which efficacy in nail psoriasis was investigated, but a case report suggests positive effect on nail psoriasis [202], and in published abstracts of subgroup analyses of the IMAGINE-1, IMAGINE-2, and IMAGINE-3 trials, brodalumab was associated with significant improvements from baseline in NAPSI scores: After the 12-week induction phase, improvements from baseline of 11.6%, 37.5%, and 46.3% were observed in the placebo, brodalumab 140 mg every 2 weeks, and brodalumab 210 mg every 4 weeks, respectively [203].

Certolizumab Pegol

Certolizumab pegol is an anti-TNF biologic with a history in treatment of Crohn's disease, rheumatoid arthritis, and psoriatic arthritis. Few years ago, it has been approved in Europe for treatment of psoriasis. In contrast to whole antibodies and to etanercept, certolizumab pegol does not induce antibody-dependent cell-mediated cytotoxicity or complement-dependent cytotoxicity as it does not have an Fc fragment. Efficacy of certolizumab pegol was already known from the RAPID-PsA study, an RCT investigating certolizumab pegol in psoriatic arthritis patients in which psoriatic nail involvement was a secondary endpoint [204]. Four-year follow-up data from this showed a total resolution rate for nail psoriasis (modified NAPSI-100) of 65% [205]. This study convincingly shows that sustained efficacy on nail psoriasis is possible with this biologic. The concomitant use of a conventional disease-modifying antirheumatic drug (methotrexate, sulfasalazine, leflunomide) in these psoriatic arthritis patients did not or only minimal influence the results on the nails [206]. Data on nail psoriasis from CIMPASI-1 and CIMPASI-2 phase 3 trials have been presented at the 2019 congress of Skin Inflammation and Psoriasis International Network but are not published yet in a peer-reviewed journal. These data showed total nail disease resolution for approximately two-thirds (66.2%, $n = 133$) of chronic plaque psoriasis patients with nail disease at 48 weeks of treatment.

Etanercept

Etanercept is a fusion protein of the TNF receptor and Fc end of the IgG1 antibody, which binds with and antagonizes the action of TNF-α. It is approved for the treatment of rheumatoid arthritis, juvenile rheumatoid arthritis, ankylosing spondylitis, psoriatic arthritis, and plaque psoriasis. Its efficacy in nail psoriasis has been shown in many studies [3]. New data on etanercept in treatment of nail psoriasis are available from comparative studies with ixekizumab [207], which are discussed in the section "Studies involving more than one biologic."

Golimumab

Golimumab is a human monoclonal anti-TNF-α antibody that has a registration for the treatment of psoriatic arthritis but not for plaque psoriasis. In the GO-REVEAL study, an RCT in psoriatic arthritis patients, nail involvement was a secondary endpoint [208]. Approximately half of the patients were also taking methotrexate. In patients treated with a normal dose of golimumab 50 mg every 4 weeks, improvement was reported both in NAPSI (−43%) and PGA (−48%) at 24 weeks. Target NAPSI improvement was even slightly higher (−52%).

Guselkumab

Guselkumab is a monoclonal antibody that targets the p19 subunit of IL-23. It is FDA and EMA approved to treat moderate-to-severe plaque psoriasis in adults. The VOYAGE1 and VOYAGE2 trials compared guselkumab with adalimumab and will be discussed in the section "Studies involving more than one biologic." In summary, improvement in fingernail psoriasis did not differ between both treatments [209].

Infliximab

Infliximab is a chimeric anti-TNF-α IgG1 monoclonal antibody that is comprised of human antibody constant regions and murine variable regions. It was approved in the US in 1998 for the treatment of Crohn's disease. Thereafter, infliximab has had its indications expanded, and in 2005/2006, it became available for the treatment of psoriatic arthritis and plaque psoriasis. The chimeric character of infliximab may result in a higher formation of neutralizing antibodies than occurs with fully human(ized) antibodies. Concerns related to the formation of these antibodies are infusion reactions, occurring in 16% of infliximab-treated patients, and the decreased efficacy of infliximab over time, which may require increased infusion frequencies and higher doses to maintain a clinical response and disease control. Infliximab dose escalation was likely to be effective in nail psoriasis patients with loss of efficacy to standard-dose therapy, suggesting that dose escalation may be a useful therapeutic option for these patients [210].

Several studies have proven the beneficial effect of infliximab on nail psoriasis, both in psoriatic arthritis and plaque psoriasis patients [3]. One recent report from prospective postmarketing surveillance confirmed efficacy of infliximab in Japanese patients with nail psoriasis [211]. Also, recent case reports show that infliximab still may be indicated in certain patients with nail psoriasis. A very fast effect of infliximab treatment was confirmed in a patient suffering from psoriatic onycho-pachydermo-periostitis, who experiences pain relief within 30 min after the injection and restoration of movement in her joints within 2 h after injection [212]. Another excellent response to infliximab was reported by Watabe et al. in a patient suffering from adalimumab-resistant childhood-onset psoriatic onycho-pachydermo-periostitis [213].

Ixekizumab

Ixekizumab is a humanized monoclonal antibody against IL-17A, which has been approved for the treatment of patients with moderate-to-severe plaque psoriasis and has shown benefits for the treatment of nail psoriasis [214]. Excellent results have been reported in early trials: Complete clearance of the nails was achieved in 51% of patients at week 68 [214]. A comparative study of ixekizumab with etanercept (UNCOVER 2 and UNCOVER 3) is discussed below in the section "Studies involving more than one biologic" [207]. Several subgroup analyses from these studies were published. One showed that also in nonresponders to etanercept, excellent improvement of nail psoriasis was measured after switching to ixekizumab [215]. Another subgroup analysis included 809 patients with fingernail psoriasis [216]. At week 60, complete clearance was achieved in more than 50% of ixekizumab-treated patients. A 3-year follow-up from the UNCOVER 3 study evaluated the long-term efficacy of ixekizumab [217]. Based on intention to treat method, at week 156, the percentage of patients remaining free of nail psoriasis was 62.4%, rather similar to the percentage at week 60. A limitation of the UNCOVER studies is the liberal definition of nail psoriasis, defined as NAPSI >0. This makes achievement of NAPSI100 easier than if a more realistic minimal NAPSI would have been used for inclusion in this nail psoriasis subgroup analysis [218].

A Japanese single-arm, open-label study with ixekizumab in patients with severe plaque psoriasis, erythrodermic psoriasis, and generalized pustular psoriasis confirmed efficacy on nail involvement [219]. In the three groups, the mean NAPSI improved to 74%, 68%, and 67%, respectively. Based on the available studies with IL-17A inhibition using ixekizumab, this treatment appears to be a very effective short-term and long-term treatment for nail psoriasis.

Risankizumab

Risankizumab is a humanized monoclonal antibody targeting IL-23A which has been approved for treatment of moderate-to-severe plaque psoriasis. Little is known about its efficacy in treating nail psoriasis. One abstract has been published which evaluated the efficacy of risankizumab compared with ustekinumab in treating nail psoriasis using data from the UltIMMa-1 and UltIMMa-2 trials in patients with moderate-to-severe plaque psoriasis [220]. At week 52, patients on risankizumab showed more reduction in NAPSI (−66%) than patients on ustekinumab (−46%). More data and full peer-reviewed publications are needed to draw conclusion on the potential role of risankizumab in nail psoriasis.

Secukinumab

Secukinumab is a fully human IgG1κ monoclonal antibody that selectively targets IL-17A, with recognized efficacy in treating psoriasis. Secukinumab showed promising results in available studies in psoriasis patients with relevant nail involvement. Its efficacy in nail psoriasis had initially been suggested from a case series of 15 patients [221] and was confirmed in the TRANSFIGURE study [222]. The TRANSFIGURE study included patients with moderate-to-severe plaque and moderate-to-severe nail psoriasis. Moderate-to-severe nail psoriasis was defined by realistic fingernail NAPSI ≥16 and ≥4 fingernails involved. At week 16, NAPSI improvement was −45.3%, −37.9%, and −10.8% for secukinumab 300 mg, 150 mg, and placebo, respectively. From week 16 onward, no placebo arm was included anymore, but improvement continued to week 32 in secukinumab-treated patients: NAPSI improvements were −63.2% and −52.6% for secukinumab 300 mg and 150 mg, respectively. This clinical improvement was accompanied by significant improvement in QoL.

Efficacy in special subgroups of nail psoriasis patients has also been suggested. Several case reports suggest that secukinumab may be effective in acrodermatitis continua Hallopeau [223, 224]. Efficacy has also been reported in a pediatric patient with severe, recalcitrant nail and joint psoriasis, whose nails had not responded to topical steroids, intralesional triamcinolone, and a 10-months therapy with adalimumab [225]. Finally, the GESTURE RCT investigated the long-term (2.5-year) efficacy of secukinumab in 205 subjects with moderate-to-severe palmoplantar psoriasis, most of which also had fingernail and toenail disease [226]. According to the authors, the mean NAPSI target fingernail and target toenail score reduced in a sustained way over 2.5 years.

Tildrakizumab

Tildrakizumab has been FDA and EMA approved for the treatment of moderate-to-severe plaque psoriasis. Two RCTs (reSURFACE 1 and 2) have demonstrated the effectiveness of tildrakizumab, a high-affinity, humanized, IgG1k, anti-IL-23 monoclonal antibody, for treating moderate-to-severe plaque psoriasis [227]. Impact on nail psoriasis has not been investigated in these trials.

Ustekinumab

Ustekinumab is a human monoclonal IgG antibody that blocks IL-12 and IL-23 and has proven efficacy in treating psoriatic nail disease in several studies, including an RCT (PHOENIX 1) [228]. In this study, the mean improvement with 45 mg of ustekinumab in NAPSI scores from baseline to week 24 was 46.5%. In the South Korean open-label MARCOPOLO study, ustekinumab was administered over a period of 52 weeks. A post hoc analysis of patients with nail involvement showed at week 28 NAPSI improvement rates for the PASI75 and PASI90 responders of 25% and 63%, respectively [229]. At week 52, PASI75 and PASI90 response corresponded to 42% and 71% NAPSI improvement rates, respectively. In another prospective study from South Korea, 13 patients with moderate-to-severe plaque psoriasis and nail involvement were treated with ustekinumab for 52 weeks [162]. The mean NAPSI scores had improved to 37% at week 52, which was not significant in this small group of patients. However, the improvement was significant using the N-NAIL, a more responsive nail scoring system which also corresponds better with clinical-assessed severity than

the NAPSI does [161]. Efficacy of ustekinumab in a patient with severe nail fold psoriasis has also been reported [151].

Studies Involving More Than One Biologic

It is very hard or even impossible to conclude which drug is most effective for treating nail psoriasis, even since most biologics are studied in well-designed randomized controlled trials. Results of these studies are impossible to compare because studies use many variants of the NAPSI, use other scoring systems, have different inclusion criteria for nail patients, have differences in the investigated population (plaque psoriasis or psoriatic arthritis), investigate monotherapy or allow to use other oral antipsoriatic drugs, and differ greatly in duration of follow-up. Because of these differences, it is essential to have comparative studies which evaluate efficacy on nail psoriasis of two or more compounds in a fair setting which allow to draw conclusions. Some comparative studies are available. Efficacy of guselkumab, an anti-IL-23 monoclonal antibody, has been compared with the anti-TNF compound adalimumab in the VOYAGE-1 study [230]. At week 16, significant improvement of target NAPSI was seen in patients on guselkumab (−34%) and on adalimumab (−38%). At weeks 24 and 48, target NAPSI improvement with guselkumab was 50% and 68%, respectively. Target NAPSI improvements with adalimumab were similar: 49% at week 24 and 61% at week 48. The percentage of patients who improved from mild to severe fingernails involvement as determined by PGA to no or minimal nail involvement at week 24 was 79% with guselkumab and 57% with adalimumab. At week 48, these percentages were 76% and 62%, respectively. Only the PGA improvement at week 48 was significantly better for guselkumab than for adalimumab. A secondary analysis was done on pooled data of the VOYAGE1 and VOYAGE2 study [209]. This analysis evaluated data of 928 patients with fingernail psoriasis that had been treated for 24 weeks. Both adalimumab and guselkumab were superior above placebo, but the magnitude of improvement did not differ between the two biologics.

A post hoc analysis of the UNCOVER-3 study evaluated the efficacy of ixekizumab versus etanercept versus placebo on significant nail involvement (NAPSI >16) in plaque psoriasis patients [207]. At week 12, ixekizumab resulted in a NAPSI reduction of 40%. At this very early time point, etanercept and placebo were significantly less effective with NAPSI reductions of 28% and −4.7%, respectively. At week 12, all patients were assigned to open-label ixekizumab through week 60. By weeks 24 of ixekizumab 80 mg every 4 weeks, 30% exhibited no signs of nail involvement anymore. This improvement persisted over the observation period. At week 60, a mean 86% NAPSI reduction was observed and 50% exhibiting no nail involvement anymore. A subgroup analysis of the same UNCOVER 3 study included only the 809 patients with fingernail psoriasis [216]. At week 12, complete resolution of fingernail psoriasis was observed in a significantly higher percentage of patients receiving a normal dose of ixekizumab (19.7%) than placebo (4.3%) or etanercept (10.2%). From the UNCOVER-3 study, it is clear that ixekizumab treatment results in a fast and high improvement of nail psoriasis in plaque psoriasis patients. It also shows that etanercept is slower in its action on nail psoriasis. However, since NAPSI improvement with etanercept was still increasing at week 12, it is not possible to conclude that after prolonged use, etanercept would have been less effective.

Laser Treatment

Laser treatment is an emerging physical therapy option claiming an indication in increasing numbers of skin and nail disorders. In nail psoriasis, it is primarily administered using a 595-nm pulsed dye laser (PDL) or long-pulsed 1064-nm (Nd:YAG) laser. Studies focused on laser treatment of nail psoriasis and have been reviewed [3, 231, 232]. Excellent results were reported, but the design and quality of the studies often were not convincing. Subungual hyperkeratosis and onycholysis have been reported to be the most responsive to therapy, while nail pitting was most resistant. Side effects of laser therapy are rather

frequent and include severe pain, purpura/petechiae, and hyperpigmentation.

In the past years, some new studies on laser treatment in nail psoriasis have been published. Arango-Duque et al. did an intrapatient left-to-right controlled study comparing PDL (pulse duration of 0.4 ms, 6 J/cm^2, beam diameter of 7 mm) plus calcipotriol betametasone gel versus Nd:YAG (beam pulse duration of 35 ms, 40 J/cm^2, beam diameter of 5 mm) plus calcipotriol betamethasone gel [233]. All patients showed improvement in nail bed and nail matrix psoriasis. The mean NAPSI declined to 44%, from 34.9 to 19.4. There was statistical difference neither between the reduction in nail bed and matrix NAPSI nor in the treatment with PDL versus Nd:YAG. Unfortunately, this study cannot clarify if the improvement is caused by the laser treatment, by calcipotriol betamethasone gel, or just by regression to the mean.

Similar improvement in NAPSI were reported by Peruzzo et al., who used PDL (4-week intervals, spot size 7 mm, pulse duration 0.45 ms, fluence 6 J/cm^2) but did not include any comparator [234]. Contrary to improvement in NAPSI, QoL did not improve. The authors admit that despite a significant reduction in the NAPSI score, the improvement in nail aspect was only noticed by a little over half of the patients, suggesting that the change was not as obvious or did not meet patients' expectations.

Youssef et al. published the first study evaluating the effect of PDL on nail psoriasis in which the control nails did not receive any treatment. Half of the involved fingernails were monthly treated with PDL on the nail plate and proximal nail fold (fluence 8 J/cm^2, pulse duration 1.5 ms, spot size 7 mm), and half of the nails were left untreated as the control arm of the study [235]. NAPSI was determined at baseline after 3 months and at month 7. The decrease in the matrix, nail bed, and total NAPSI scores of about 80% in the treated nails at month 3 and month 7 was statistically significant compared to pretreatment scores and to control nails' scores. There was no statistically significant difference between the nail bed response and the nail matrix response in the treated nails.

The long-pulsed Nd:YAG laser (6 mm, 10 J/cm2, pulse duration 15 milliseconds with 1.5 Hz repetition rate) has also been reinvestigated recently in nail psoriasis in an uncontrolled study in 16 patients [236]. Nails were treated for three sessions with long-pulsed 1064-nm Nd:YAG laser once monthly. The mean baseline NAPSI score was 26. The mean NAPSI after the first, second, and third treatment sessions were 22, 13, and 5.7, respectively. At the end of the three treatment sessions, both nail bed and matrix lesions significantly responded to Nd:YAG laser treatment. Drawing conclusions from this study is limited by lack of a control treatment.

Summarizing these results, it is possible that laser treatment of nails has some beneficial effect in nail psoriasis. However, QoL seems not to improve, nor is the improvement noticed by a vast majority of treated patients [234]. A randomized study comparing laser treatment with sham laser treatment is urgently needed to justify this painful treatment in patients with nail psoriasis.

Radiotherapy

Radiotherapy is rarely used in the daily clinical care of patients with nail psoriasis. Nevertheless, cases and clinical trials with superficial radiotherapy, Grenz ray therapy, and electron beam therapy have been reported [3]. Improvement of nail psoriasis was generally limited and only temporary. Safety concerns are another reason why radiotherapy is not a realistic option for the long-term treatment of nail psoriasis. Results of 27 courses of Grenz ray therapy for the treatment nail psoriasis has been reported by Fenton and Dawe [237]. Clearance was reported in one patient. No change or minimal improvement was the conclusion in the vast majority of patients.

Also, experimental treatment with high-dose-rate brachytherapy with custom-made micro applicators has been reported in nail bed psoriasis [238]. The hypothesis was to apply high-dose-rate brachytherapy treatment using ^{192}Ir source in order to stimulate the T cells for "desirable" immune response. Three patients received monthly subungual injections that caused signifi-

cant pain and discomfort in both hands. The treatment outcome was reported to be favorable with disappearance of symptoms in all three patients within the first 6 months.

Conclusion

Nail psoriasis encounters greatest interest of the scientific community, resulting in new and promising therapeutic developments but also in more and more insight in pathogenic mechanisms. In spite of these major developments, several aspects of nail psoriasis need more progress. For example, topical therapies for nail psoriasis are available, but convincing clinical efficacy often is disappointing. Furthermore, development of effective treatments needs improved, generally accepted, and applied endpoint outcome measurement through a consensus process involving relevant stakeholder groups. Finally, the mechanism and relevance of nail psoriasis for early detection of potential destructive psoriatic arthritis need fresh and unbiased attention of both the dermatology and rheumatology community. If all these aspects get the attention they deserve, in the next decade, all small steps will result in a giant leap for all patients suffering from nail psoriasis.

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Nail Lichen Planus

13

Bianca Maria Piraccini, Michela Starace, and Matilde Iorizzo

Abbreviations

LP	Lichen planus
NLP	Nail lichen planus
YNS	Yellow nail syndrome

Introduction

Nail lichen planus (NLP) is a benign inflammatory condition described in about 10–16% of patients affected by skin, scalp, or mucosal lichen planus (LP) [1]. When it affects only the nail unit, it is rather uncommon (2% of all nail disorders). NLP is more frequent in adults, with the same frequency in both sexes, than in pediatric population, where males are affected more than females [2]. According to the literature, individuals aged between 50 and 70 years are those most commonly affected (with a peak around 50 years). In children, isolated NLP is rare and has a more benign course [3, 4].

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Nail involvement by LP may precede or follow the development of cutaneous or mucosal lesions. Oral involvement is the more frequent association with NLP (25% of cases) [1], while skin or scalp LP are rarely associated with the nail signs. NLP causes considerable cosmetic discomfort to patients and impaired manual function, and patients always complain of a reduced quality of life.

Pathogenesis

Evidences suggest that LP is an autoimmune disease specifically mediated by cytotoxic T CD8+ cells and plasmacytoid dendritic cells and that nail abnormalities are caused by a damage to nail epithelia basal keratinocytes that express autoantigen on their surface [5]. The lichenoid inflammatory infiltrate produces different signs according to the altered function of the involved area. Usually, several/all nails are involved with different degrees of severity, more evident in the thumbs. Other autoimmune skin disorders may be occasionally associated, especially in children, including alopecia areata, psoriasis, and thyroiditis [3]. A family history can rarely be elicited.

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Clinical Features

Five possible clinical presentations have been described in the literature [1]:

1. "Typical" NLP: 80% of the cases
2. Trachyonychia: 8% of the cases
3. Idiopathic atrophy of the nails: less than 5% of the cases
4. YNS-like LP: rare
5. Bullous/erosive LP: extremely rare

Another rare type of NLP is represented by nail degloving, a post-inflammatory avulsion of the nail epithelia [6].

"Typical" nail matrix LP is the most common type of NLP (Fig. 13.1). Involvement of the nail matrix gives rise to surface alterations like thinning, fragility, longitudinal ridging, and fissuring. This longitudinal pattern is quite characteristic. Severity of symptoms may vary, with patients who only show mild fissures of the nails and others where nail thinning produces a short nail plate with deep fissured margins. These signs of nail matrix LP are usually observed only in the fingernails and are more rare in the toenails, where LP produces marked nail plate thickening in most of the patients (Fig. 13.2). Another typical sign of nail matrix LP is dorsal pterygium, a V-shaped scarring of the proximal nail fold that extends onto the nail plate (Fig. 13.3). It is a sign of focal nail matrix destruction, resulting in a permanent scar and unresponsive to any treatment. Although typical of NLP, pterygium is not a common finding. Pterygium can affect one digit or multiple digits. Multiple pterygia can also be observed in a single digit. Pterygium development does not depend on duration of the disease [7].

When LP involves the nail bed, it causes onycholysis with or without subungual hyperkeratosis, which are not diagnostic for this disorder (Fig. 13.4). If the onycholysis is severe, the nail plate may shed resulting in nail bed atrophy (disappearing nail bed syndrome) and permanent anonychia. Nail bed hyperkeratosis, when focal, may be responsible for tenting of the nail plate, resulting in a nail plate lifted and split into two parts giving the appearance of a pup tent.

Fig. 13.1 "Typical" nail matrix LP of the fingernails: nail thinning, longitudinal ridging, and fissuring

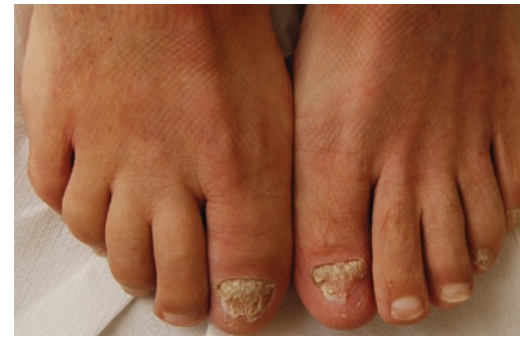

Fig. 13.2 Toenail typical LP with nail thinning and longitudinal fissuring

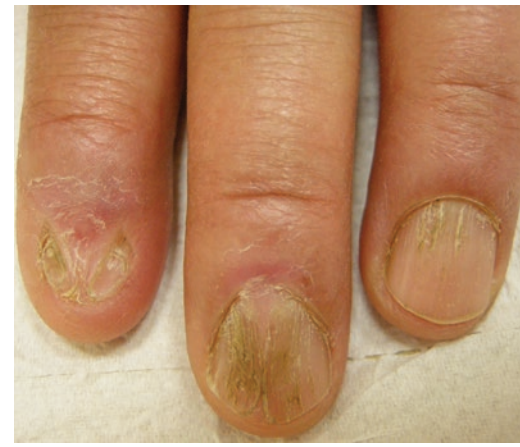

Fig. 13.3 Dorsal pterygium of the second fingernail: v-shaped extension of the proximal nail fold toward the nail bed due to absence of nail plate

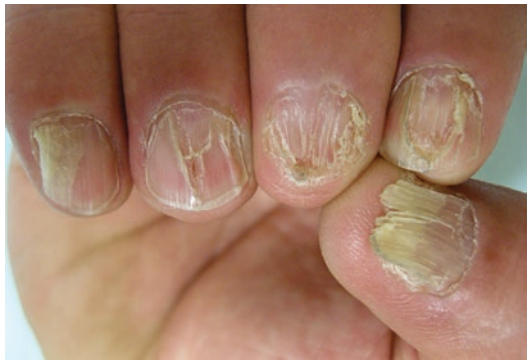

Fig. 13.4 LP of the nail bed of the first and fifth fingernails, causing onycholysis and subungual hyperkeratosis

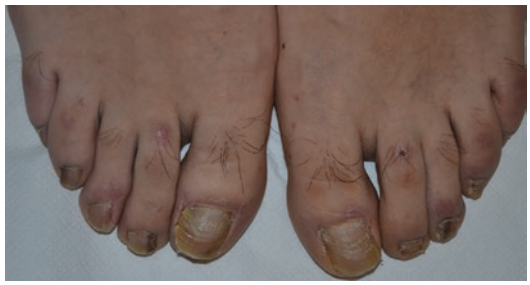

Fig. 13.5 LP of the proximal and lateral nail fold with Wickham striae

LP of the nail bed may rarely cause hypertrophic LP, characterized by diffuse nail thickening due to homogeneous nail bed hyperkeratosis. Involvement of the proximal and lateral nail fold occasionally causes Wickham striae (Fig. 13.5). However, a nail bed LP alone is rare; matrix NLP is in fact frequently associated.

In most cases, the diagnosis of NLP can be made clinically, but in doubtful cases, a biopsy is required. Site of biopsy should be chosen depending on clinical signs at diagnosis.

When LP involves the nail matrix in a mild and diffuse way, it produces trachyonychia [8] that it is also known as 20-nail dystrophy because it usually involves all 20 nails. However, there are some cases involving only one or few nails. Children are usually more affected than adults.

Trachyonychia is characterized by inflammation of the proximal nail matrix: a severe and persistent inflammation produces the opaque

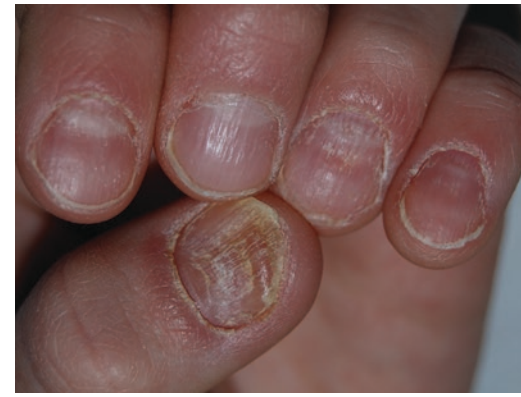

Fig. 13.6 Trachyonychia due to LP: opaque nail plate due to fine longitudinal striations covered by minute scales and mild nail thinning

variant (sandpapered, lusterless, and rough nails, sometimes superficial scaling and longitudinal ridging) (Fig. 13.6); a milder and more intermittent inflammation is responsible for the shiny variant (numerous small punctate depressions are distributed in a geometric fashion reflecting the light and giving a shiny appearance to the affected nails).

Differential diagnosis with trachyonychia due to alopecia areata or psoriasis is not clinically possible but requires a pathological study of the nail matrix after a biopsy. LP is responsible for trachyonychia in about 16% of the biopsied cases [8]. Even when caused by nail LP, trachyonychia is always a benign condition and does not produce scarring or anonychia [8]. The insult to the proximal nail matrix keratinocytes impairs their maturative and differentiative activity without interrupting their mitotic activity, thus explaining why this is not a scarring disorder.

In idiopathic atrophy of the nails, there is, instead, an acute and rapid development of pterygium in several nails with progressive atrophy, in the absence of subjective symptoms or other cutaneous signs. This variety of lichen planus is very rare, almost exclusively observed in Asians, and may sometimes be hereditary [9]. The involved digits show total or subtotal absence of the nail plate with dorsal pterygium. The proximal nail fold may show atrophy and teleangectasias (Fig. 13.7).

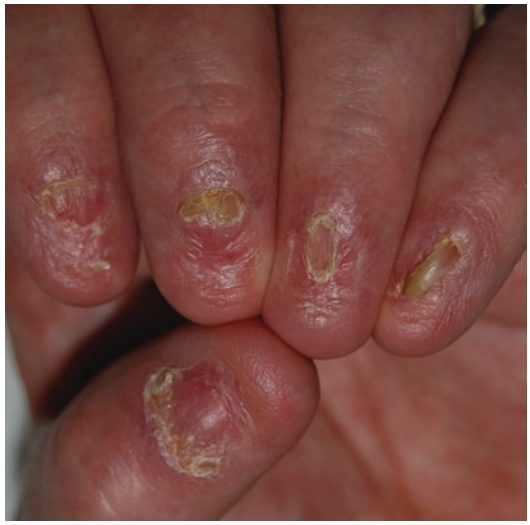

Fig. 13.7 Idiopathic atrophy of the nails with subtotal absence of the nail plate and dorsal pterygium

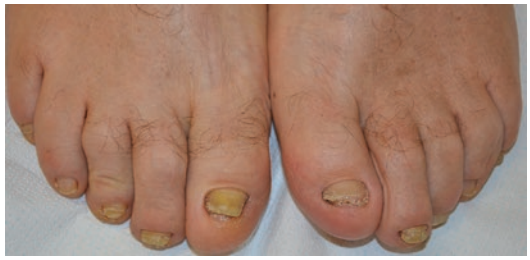

Fig. 13.8 YNS-like LP characterized by marked nail thickening and a yellow nail color

The YNS-like LP variant is a particular clinical presentation of NLP of the toenails, characterized by marked nail thickening and a yellow nail color, with features mimicking the YNS [10] (Fig. 13.8). Only the evaluation of fingernails, presenting the typical NLP features, may suggest the correct diagnosis.

Another rare type of NLP is the erosive variant, where bullous and/or ulcerative lesions develop in the matrix and bed resulting in complete shedding of the nail plate and nail scarring (Fig. 13.9) [11]. Bullous/erosive LP of the nails usually affects the toenails and may spread to the periungual and plantar skin.

Other possible clinical signs described in NLP include pigmentary changes, i.e., longitudinal melanonychia (Fig. 13.10) [12] and longitudinal erythronychia (Fig. 13.11) [13]. Red spots in the

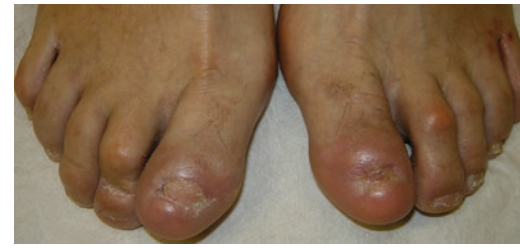

Fig. 13.9 Erosive LP with bullous and ulcerative lesions and nail scarring with complete nail loss

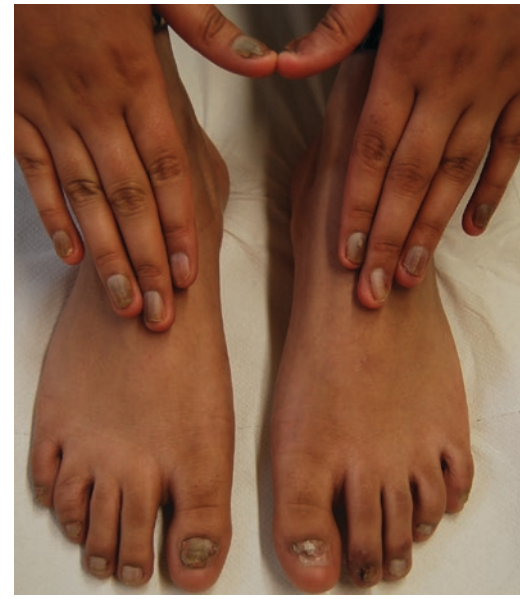

Fig. 13.10 Pigmented LP with melanonychia

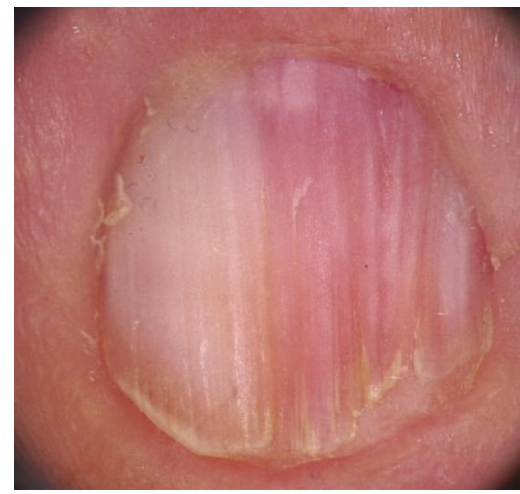

Fig. 13.11 Onychoscopy of typical NLP: longitudinal fissuring and longitudinal erythronychia

lunula (mottled erythema) are reported in about 25% of cases and correspond to dilated and tortuous vessels in the papillary dermis of the distal matrix [14].

Differential Diagnosis

The diagnosis of NLP may be easy in a patient with LP of the skin or the oral mucosa but might be difficult when the disease is limited only to the nails. Longitudinal ridging and fissuring are typical of nail LP, but nail psoriasis may produce similar changes. Systemic amyloidosis may involve the nails producing clinical signs resembling those of NLP, usually associated with splinter hemorrhages [15]: a longitudinal nail biopsy with Congo red staining is then needed to detect amyloid deposits in the nail matrix and bed. Dorsal pterygium, longitudinal ridging, and distal splitting of the 20 nails are also typical features of graft versus host disease, but the history of the patient is generally diagnostic [16]. Dorsal pterygium can have a traumatic cause, due to accidental or surgical trauma, ischemic cause, or bullous diseases, and this is also reported by the patient.

Diagnosis

- Onychoscopy (dry technique) may help in the diagnosis of NLP as it enhances visualization of the longitudinal fissures of the nail plate surface (Fig. 13.11). In dorsal pterygium, onychoscopy shows the distal extension of the dorsal skin of the digit that splits the nail plate into two or completely substitutes the nail plate (Fig. 13.12). Mottled erythema of the lunula is also better visualized with onychoscopy. Wickham striae maybe easily seen by dermoscopy in proximal nail fold LP when present (Fig. 13.13).
- When the clinical presentation is suspicious, a nail biopsy is recommended to avoid delayed diagnosis. A longitudinal biopsy is preferrable, as the nail matrix is involved in the majority of the cases. The histopathological confirmation of the diagnosis is also helpful to explain to the patient the disease course and increase patient's acceptance of therapy. A monodactylic presentation should always be investigated to rule out amelanotic melanoma, especially in adult patients. The pathology of NLP shows a dense band-like infiltrate in the matrix/ben dermis composed mostly of lymphocytes, numerous melanophages in the superficial dermis, a linear dermo-epithelial junction, and irregular epithelial hyperplasia with diffuse granulosis in the matrix [17]. Recently nail plate thinning has been described as a "frayed nail plate" due to loss of cohesion of individual orthokeratotic onychocytes [18].

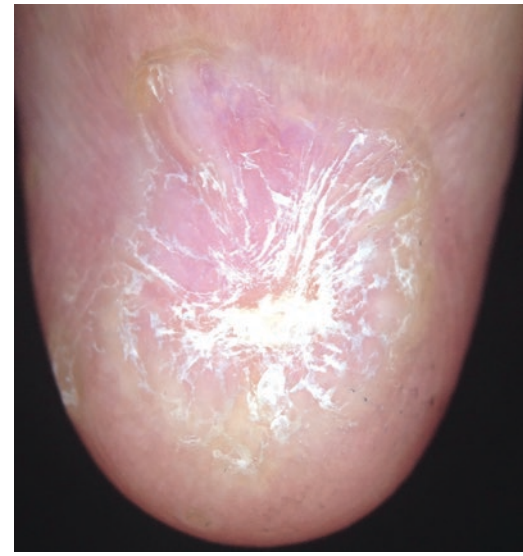

Fig. 13.12 Onychoscopy of dorsal pterygium

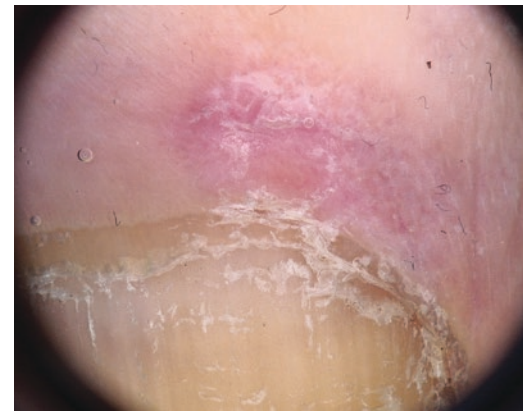

Fig. 13.13 Onychoscopy of LP proximal nail fold of patient of Fig. 13.5, showing Wickham striae

Treatment

Treatment of NLP is difficult with a high rate of relapses and recurrences, a lack of cure for some irreversible features, and no definitive treatment guidelines or significant evidence-based studies available. Not all types of NLP require therapy: while treatment is mandatory for typical NLP and bullous NLP, it is not effective in idiopathic atrophy of the nails, where scarring is not reversible, and not required in trachyonychia, which is always a benign condition that often resolves spontaneously with age.

Treatment should always be selected according to the severity of the clinical presentation, number of affected nails, presence of concomitant LP in other body areas, comorbidities, previous unsuccessful/successful treatments, age, and quality of life. Early treatment is mandatory in order to prevent irreversible nail damage due to rapid evolution of this disease.

Optimal therapy is still lacking, but systemic or intralesional high potency steroids can be considered the treatment of choice [19].

- Intralesional steroids (triamcinolone acetonide 5–10 mg/mL diluted in saline solution) can be injected into the matrix or bed at monthly intervals for 5–6 months when up to three nails are involved, until complete clearing or marked improvement of nail signs and then tapered off. Five to six injections are necessary to achieve visible improvement.
- Systemic steroids (intramuscular triamcinolone acetonide 0.5 mg/kg per month) are to be preferred when several/all nails are involved or in patients who refuse intralesional injections. They can be utilized both in adults and in children with NLP with optimal tolerability. Treatment should last 5–6 months and then be tapered off. Assessment of response to therapy can be done as soon as after 2 months of treatment by looking at the proximal 3 mm of the nail plate with a dermatoscope, in order to assess the aspect of the newly formed nail plate that may still grow with longitudinal fissures (failure) or be smooth and shiny (response). If no clinical response after 6 months is achieved, a change of treatment should be considered, and tapering is not necessary.

Treatment with steroids is effective in 2/3 of the patients, producing arrest of progression or total or partial regression of nail symptoms [7]. The only study that performed a long-term follow-up of a series of patients with NLP did not find any factor (age, gender, duration, severity, associated skin/mucosal LP) that can predict which patients would benefit from treatment and which not [7]. Fingernails respond better and quicker than toenails, which may remain thick for a long time. Unfortunately, relapses after cure occur in about 60% of patients [7].

- Acitretin 0.3 mg/kg/day can be used in patients not responding to systemic steroids. Side effects related to the drug include nail softening and fragility, especially evident at high dosages [1].
- Oral alitretinoin has recently been shown to be effective in patients with NLP [20, 21]. An initial dose of 30 mg daily can be used for the first 3 months and then be reduced to 10 mg daily to maintain long-term efficacy.
- Alterative systemic therapies are azathioprine 100 mg daily, in association with systemic steroids in order to increase response to therapy [7], cyclosporine 3–5 mg/kg/day, mycophenolate mofetil 1000 mg/twice a day.
- New treatments include etanercept [22], the Janus-kinase inhibitor 1/3 tofacitinib [23, 24], and bath PUVA [25].

Prognosis

The prognosis of LP is highly variable. Typical NLP is slowly progressive, and pterygium formation takes several months to present but may not occur at all. Some patients may have a more rapid worsening of nail signs, until atrophy.

In general, NLP has a negative long-term prognosis in a considerably high percentage of patients, if we consider patients who do not respond the initial steroid treatment (20% of cases) and those with nonresponsive relapses

(about 30% of the cured patients). Furthermore, patients who do not respond to systemic steroids are unlikely to benefit from other therapies [7].

Less than 10% of the patients who respond to therapy do not heal completely, but maintain mild nail lesions, consisting in small superficial fissures of the nail plate distal margin and longitudinal bands of leukonychia.

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What's New in Pediatric Nail Disorders?

14

Maureen Tasia and Bertrand Richert

Abbreviations

HFMD	Hand, foot and mouth disease
LM	Longitudinal melanonychia
NAPSI	Nail Psoriasis Severity Index
NMN	Nail matrix nevius
NPS	Nail-patella syndrome
PASI	Psoriasis Area Severity Index
PC	Pachyonychia congenita
SE	Subungual exostosis
YNS	Yellow nail syndrome

Introduction

Nail disorders in children can be classified into seven categories: physiologic, congenital and/or hereditary, infectious, inflammatory, traumatic or mechanical, neoplastic, systemic, and/or iatrogenic [1]. Most pediatric nail conditions are benign but are a source of anxiety for parents or physicians inexperienced in onychology and may be a cosmetic issue or a cause of functional impairment [1, 2]. To date, very few studies have been conducted to determine the overall prevalence of nail disorders in children [3–5]. This prevalence has been estimated at 11.1% and 6.8% in two studies [3, 4]. A very recent study examined the span of nail conditions in a pediatric onychology center and highlighted the ten most frequent diagnoses (Table 14.1) [6].

This study also demonstrated that some diagnoses were more frequently encountered depending on the age category (Table 14.2). Another publication has classified nail diseases in children according to age [7].

This chapter collects the recent findings and updates found in the literature on children's nail disorders. This review includes the most relevant articles from the last 5 years. Search engines were Google Scholar and the Medline database through PubMed and MeSH. Keywords included "nails," "children," "infants," and "teenagers," as well as specific keywords for many nail disorders.

Table 14.1 Ten most frequent diagnoses in a pediatric nail consultation [6]

1.	Fever-related Beau's lines or onychomadesis
2.	Trachyonychia
3.	Longitudinal melanonychia
4.	Congenital malalignment of the great toenail
5.	Podiatric-related chronic trauma
6.	Onychomycosis
7.	Acute trauma and *sequelae*
8.	Congenital hypertrophy of the lateral nail folds
9.	Acute paronychia
10.	Juvenile ingrown nails

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Table 14.2 Most frequent diagnoses according to age [6]

0 to <2 years old	Congenital hypertrophy of the lateral nail Congenital malalignment of the great toenail
2 to <6 years old	Fever-related Beau's lines
6 to <12 years old	Trachyonychia Longitudinal melanonychia
12 to <18 years old	Juvenile ingrown nails Acute trauma and *sequelae* Podiatric-related chronic trauma Longitudinal melanonychia

Physiologic Alterations

Very few papers have described physiologic nail alterations in children, especially in newborns. A recent study from Chinazzo et al. described the normal nail features in newborns. It showed that koilonychia, onycholysis, and onychoschizia were frequent findings on toenails, while the absence of lunula was a usual feature of both finger- and toenails. The authors also reported an apparent hypertrophy of the proximal nail fold of the hallux in 1/3 of the toddlers and of the lateral folds of the hallux in 3/4 of the newborns. This hypertrophy was accentuated by koilonychia and a triangular shape of the nail plate. All dark-skinned newborns showed hyperpigmentation of the proximal fold of both hands and feet, especially between 2 and 6 months, that faded before the age of 1 [8].

One article reviewed the literature on koilonychia, which is a common feature on toenails in infants. Although mostly transient and idiopathic in young children, some familial and syndromic cases have been reported [9].

Key Points

- Koilonychia, onycholysis, and onychoschizia are frequent findings on toenails in newborns, as well as the absence of lunula on both finger- and toenails.

Congenital Disorders

Congenital Malalignment of the Great Toenails

This entity is probably underdiagnosed, and most of the recent publications are case reports [10–13]. Congenital malalignment usually appears at birth or during the first years of life [10]. Mean age for medical consultation is 3 years old [6]. However, a few studies reported cases of great toenail malalignment with onset in adolescence or young adulthood without any history of nail surgery or acute trauma, raising the possibility of a late-onset presentation of this condition [11, 14]. Congenital malalignment of the great toenail spontaneously improved in 58% of a recent case series of 25 patients, similar to the 50% rate quoted in the literature [6, 15]. Clinical observation with photographic follow-up along with podiatric care is the rule. For severe forms, or those that don't resolve spontaneously, surgical realignment may be considered to avoid unsightly and persistent nail dystrophy [10, 16]. In the most recent series, four patients underwent a whole nail unit rotation surgery, with an improvement of the nail dystrophy in three cases [6].

Congenital Hypertrophy of the Lateral Nail Folds

Congenital hypertrophy of the lateral nail folds affects children around the age of 1 (Fig. 14.1). Great toenails are mainly involved, both in 67% of cases. Spontaneous improvement occurs in around 3/4 of cases, reason for which conservative care and follow-up is usually sufficient. Surgery is infrequent and restricted to very prominent or recalcitrant cases [6].

Pachyonychia Congenita

Pachyonychia congenita (PC) is a group of autosomal dominant disorders resulting from mutations in one of five keratin genes [17, 18]. The last classification, validated by phenotype-

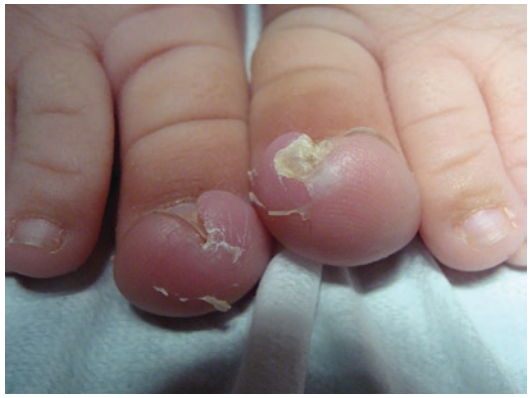

Fig. 14.1 Prominent hypertrophic medial fold in a toddler

genotype correlations, divides PC into subtypes according to the mutation found in the keratin-encoding genes KRT6A, KRT6B, KRT6C, KRT16, and KRT17 [19]. PC prevalence in Western countries is 0.9 cases per million with a worldwide PC population estimated between five to ten thousand. In a large case-cohort study of 815 patients conducted by Samuelov et al., the earliest and most common clinical feature of PC was nail dystrophy, appearing during the first year of life in most cases. The median number of affected fingernails and toenails was ten, while the mean number was 6.4 and 8, respectively. Fifty-one percent of PC patients had all 20 nails affected [18]. Nail dystrophy may be responsible for pain, infection, and functional and psychosocial impairment [17, 18]. It deeply affects social interactions and function of adolescents. Among patients with a detectable mutation, PC manifests with nail thickening and plantar keratoderma before school age in more than 3/4 of affected children, allowing early diagnosis [19]. KTR6A mutations were associated with a younger age at diagnosis and a higher number of fingernails/toenails involvement. Conversely, a lack of fingernail involvement was most commonly associated with KRT16 and KRT6B mutations [18, 20]. An increased number of affected toenails and earlier age of toenails involvement predicted fingernail dystrophy, while an increased number of affected fingernails correlated with toenails involvement. Earlier onset of toenails involvement correlated with the development of plantar keratoderma, while age of fingernail dystrophy onset and walking aids use predicted palmar keratoderma. Finally, oral leukokeratosis and natal teeth correlated with an earlier toenail involvement, while hoarseness correlated with an increased number of involved fingernails [18]. No specific histopathological feature is identified in PC nails. Parakeratosis and plasma globules are the most prominent features in both clinically affected and unaffected PC nails. The presence of onychomycosis in a nail plate does not exclude a diagnosis of PC [20]. Nail removal remains a therapeutic option and seems to have an overall positive outcome [17].

Nail-Patella Syndrome

Nail-patella syndrome (NPS) is a rare autosomal dominant condition characterized by variable nail, skeletal, renal, and ocular anomalies [21]. The incidence of NPS is usually given as 1 per 50,000, but an epidemiologically based incidence estimate is still lacking [22, 23]. LMX1B is the major gene responsible for NPS and explains around 95% of all cases [24]. To date, over 180 heterozygous mutations of LMX1B have been reported in NPS [22]. A new mutation in WIF1 gene has also been identified, suggesting a potential novel cause of NPS [24]. Mean age at the time of clinical diagnosis is 6.54 years [25]. Almost all patients have nail abnormalities, the most frequent being hyponychia. Other findings include triangular lunula, absence of lunula, anonychia, nail splitting, pterygium, koilonychia, as well as the loss of the dorsal creases in the skin overlying the distal interphalangeal joints [21, 25]. These nail changes may be present since birth and are commonly bilateral and symmetrical [25]. Each individual nail is usually more severely affected on its ulnar side [23, 26]. Thumbnails are the most affected, and the severity tends to decrease towards the little finger [23, 25, 26]. When toenails are involved, the abnormalities tend to be less severe, and the little toenail is most commonly affected [23]. Triangular lunula is a pathognomonic finding, but it is not encountered in all cases [25]. When present, it is

mainly associated with a dystrophy of the medial part of the nail, ranging from a simple longitudinal crease to pseudopterygium and median nail fracture. These findings are detectable only in forms of NPS with severe nail involvement [26]. The severity of the nail signs is unrelated to visceral involvement [25, 26].

Key Points

- Congenital hypertrophy of the lateral nail folds is a benign condition that spontaneously improves in 3/4 of cases. Surgery should be restricted to resistant cases.
- Congenital malalignment of the great toenail spontaneously improves in around 50% of cases. Clinical observation and photographic follow-up are a must. Severe cases and non-improving cases should be proposed surgery.
- Pachyonychia congenita is responsible for severe psychosocial impairment. By the age of 5, more than 3/4 of patients have nail alterations, allowing early diagnosis.
- Nail alterations are constant in nail-patella syndrome. Triangular lunula is pathognomonic but not always present.

Infectious Diseases

Periungual Warts

Periungual warts are a therapeutic challenge (Fig. 14.2). Treatment modalities include salicylic acid, cryotherapy, bleomycin, contact immunotherapy – with diphenylcyclopropenone or squaric acid dibutyl ester – and laser ablation [27]. A shorter sensitization period and a more severe sensitization reaction (characterized by a higher "erythema and blister index") contribute

Fig. 14.2 Viral warts on the finger and the upper lip of a nail biter

to a shorter time period required for a complete cure of the periungual warts with diphenylcyclopropenone immunotherapy [28]. Another type of immunotherapy that can be used is Vitamin D3 injections in an oily base, just beneath the warts, every 2 weeks for a maximum of four sessions. This new treatment seems promising. However, pain during injection is the limiting factor. It is a safe, inexpensive, and effective treatment for periungual warts [29]. Topical cidofovir is a possible alternative for recalcitrant periungual warts or those that fail to respond to the conventional treatment. Nonetheless, its high price and its limited availability are major limitations [30]. The application of a nitric-zinc complex solution (Verrutop®) twice a month on warts resulted in a complete clearance in 83.9% with excellent cosmetic results and tolerance, according to a recent study [31]. In a small case series of 11 patients, translesional bleomycin delivered via a multipuncture technique using an ablative carbon dioxide fractional laser before the application of bleomycin on the wart resulted in a complete clearance – recurrence-free for 6 months – in 70% of cases [32]. Finally, a combination of superficial shaving with photodynamic therapy also seems to be an effective and safe treatment for recalcitrant, multiple, and thick periungual warts [33].

Nail Scabies

To date, only five cases of pediatric nail scabies have been reported in the literature [34–36]. In the study of Chinazzo et al. including 47 children with confirmed scabies, a nail involvement was found in 6.4% of children, all infants. In two of the three cases, scabies was surprisingly found in a great toenail rather than in fingernails. According to Chinazzo et al., the nail area may constitute a reservoir of mites and may be a risk factor for scabies recurrence. Nails should not be overlooked during scabies treatment [34]. Some authors recommend to cut, brush, and apply a topical scabicide on the nails, even in classic scabies [35].

Acute Paronychia

Neonates with oral self-soothing behaviors may be more at risk for developing paronychia of mixed anaerobic and aerobic infections. Initial therapy with broad-spectrum antibiotics amoxicillin/clavulanate or clindamycin is suggested [37].

Onychomycosis

Onychomycosis in childhood is rare and affects approximately 0.2–2.6% of all children [38, 39]. However, an increased incidence has been reported in the pediatric population [38]. *Trichophyton rubrum* is the most commonly isolated pathogen, as in adults [39, 40]. Children are more likely to respond to monotherapy since they have thinner and faster-growing nails [41]. New topical treatments for onychomycosis have an increased nail penetration and sometimes additional delivery routes to the site of infection [42, 43]. Tavaborole may be a good candidate to treat children with onychomycosis. It penetrates the nail plate very well and is effective when used in monotherapy [41]. It was found to be safe and well tolerated in the pediatric population [44]. When a systemic treatment has to be prescribed, terbinafine is the first choice. It is recommended to perform a baseline transaminase monitoring. On a study with 261 children treated with terbinafine, the authors discovered that 12.5% of patients had grade 1 laboratory abnormalities – such as liver alterations – prior to (8.3%) or during therapy (4.2%). However, if the pretreatment' routine laboratory is within normal limits, further monitoring is unnecessary, considering the low incidence of clinically significant adverse effects, costs of laboratory tests, and patient discomfort [45].

Key Points

- Periungual warts remain a therapeutic challenge.
- Nail scabies may be a risk factor for resistance to therapy and recurrence.
- Neonates with oral self-soothing behaviors may be more at risk for developing paronychia.
- New topical treatments with better nail penetration may be used in monotherapy for onychomycosis.

Inflammatory Disorders

Nail Lichen Planus

In Goettmann et al.'s study, among 67 patients with nail lichen planus, around 11% were children [46]. In a more recent study from Morocco, among the 20 cases of nail lichen planus, amazingly 40% were children, highlighting the frequency of pediatric forms in this country [47]. Nail alterations are reported in 13.9% of children presenting with skin lichen planus [48].

Nail Lichen Striatus

In a report of seven cases by Kim et al., four were children, between 4 and 11 years old. All patients had both typical skin lesions and nail abnormalities, although lichen striatus can be limited to the nail. Nail lichen striatus usually involved a single digit. The most common nail change was longitudinal fissuring (Fig. 14.3) [49]. Iorizzo et al. described the dermoscopic features of nail lichen striatus: involvement of only one part of the nail plate with linear longitudinal fissuring, ridging, and distal splitting, especially if seen with perionychial skin lesions, is characteristic. This dermoscopic pattern may help in the diagnosis of nail lichen striatus [50]. In the study of Kim et al., most nail lesions resolved within a mean of 4 months after the initiation of a topical corticosteroid cream and 0.1% tacrolimus ointment for both skin and nail lesions [49].

Fig. 14.3 Isolated fissure on the index nail due to lichen striatus

Trachyonychia

In a recent series of 26 patients, trachyonychia mainly affected children between 6 and 12 years old, with a mean age of 8 years [6]. Biopsies for diagnostic purposes are not recommended because whatever the cause, trachyonychia doesn't lead to nail destruction [51]. A favorable evolution was observed in 75% of cases, confirming the good prognosis previously published, regardless of treatment (Fig. 14.4) [6, 51, 52]. Nonetheless, an annual photographic follow-up is usually suggested to reassure parents and their child. In a recent series, trachyonychia did not appear to regress faster in patients receiving topical treatment, in contrast with the study of Park et al., which reported a significant nail improvement in 98.6% of cases with calcipotriol/betamethasone ointment applied once daily for 6 months [6, 53].

Nail Psoriasis

The prevalence of nail involvement in psoriatic children varies widely between studies. In

Fig. 14.4 Trachyonychia. Spontaneous healing over 2 years without treatment

recent series, nail involvement was reported between 15.7% and 32.3% of psoriatic children [54–56]. This prevalence increases with age [55, 56]. Fingernails are involved more frequently than toenails [55]. The main clinical features are pitting on fingernails and onycholysis as well as pachyonychia on toenails. Other common features include Beau's lines, oil drop, paronychia, leukonychia, and splinter hemorrhages. All fingers are involved at similar frequencies, whereas the big toenails are involved twice as often as the others, suggesting a Koebner phenomenon. Nail involvement is significantly associated with male gender, palmoplantar psoriasis, and a higher PASI (Psoriasis Area Severity Index) score, indicating a more severe disease course over time [55, 56]. When comparing the mean NAPSI (Nail Psoriasis Severity Index) and the mean PASI according to nail lesions, a study found that subungual hyperkeratosis and nail fold psoriasis were significantly associated with the severity of both nail psoriasis and cutaneous psoriasis [57]. As in adults, nail psoriasis is closely associated with psoriatic arthritis [55]. Nail involvement in children is also associated with metabolic comorbidities such as abdominal obesity, overweight, or metabolic syndrome [58]. The microscopic nail features such as the presence of neutrophils and serous lakes in the nail plate have also been associated with higher PASI and NAPSI scores in psoriatic children. Nail clippings remain very useful to help the diagnosis and to rule out onychomycosis [59].

Key Points

- Nail lichen planus is rare in children, accounting for about 11% of all nail lichen planus cases.
- Nail lichen striatus is characterized by a linear longitudinal fissuring, ridging, and distal splitting of one part of the nail plate.
- Trachyonychia spontaneously improves in most cases and never leads to nail destruction, whatever the cause. Biopsies are therefore unnecessary.
- Nail psoriasis is associated with psoriatic arthritis and with a higher PASI score, indicating a more severe course of the disease.

Traumatic and/or Mechanical Disorders

Pediatric Finger Injuries/Acute Trauma

Fingertip injuries are common in children, affecting mostly boys under 5 years old, probably because of an imbalance between gross motor abilities and cognitive development [60–63]. Younger children are also naturally curious and use their hands to probe and explore their environment [62, 64]. Among all finger injuries, nail bed injuries and fractures are the most prevalent [60, 62]. Nail bed injuries can be classified as subungual hematomas, simple or stellate lacerations, avulsions, and crush injuries [65]. Crushing injury of finger by door or window is still the most common mechanism of injury among younger children and accounts for a large number of hospital admissions. The door is often closed by another child, at home, in the presence of an adult. The right hand is usually involved and the most commonly injured finger is the middle finger (Fig. 14.5) [60, 62]. Imaging rules out bone fractures [64]. The management of subungual hematomas and nail bed lacerations remains controversial. Most hematomas caused by nail bed lacerations do not usually require nail removal and repair, if the nail/nail margins are intact. Small hematomas are often left to reabsorb without treatment [66]. For larger and painful subungual hematomas, there is much debate about removal of the nail plate for repair of a nail bed laceration compared with simple trephination – i.e., the creation of a hole in the nail plate to release trapped blood [65, 66]. Satku et al. compared the results of nail removal and

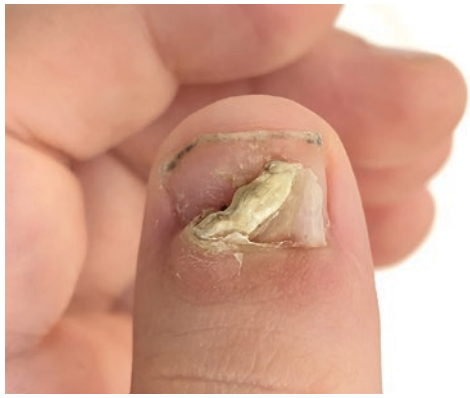

Fig. 14.5 Post-traumatic dystrophy. Horizontal duplication of the matrix

formal nail bed reconstruction with trephination of a subungual hematoma after a fingernail crush injury. They found that simple nail trephination was equal or superior to removal of the nail with nail bed repair, with significantly lower cost [61]. The rate of accidents is not reduced by the presence of adults, which highlights the need for preventive measures and health education [60, 63]. Satku et al. suggested techniques to prevent door crush injuries in children, including placing door stoppers and using plastic hinge protectors [61, 62]. The cost of prevention of fingertip injuries by using safety equipment is less than the cost of treating them [61, 63]. Sports injuries are most common among the 13- to 18-year-old age group [62].

Podiatric Disorders

Podiatric abnormalities remain underestimated and should be considered as potential causes of nail abnormalities in children. It includes toe malposition, difference in shape/size between the two feet, abnormal gait, or improper shoes. Toe malpositioning results in nail thickening, nail bed hyperkeratosis, or onycholysis, which may mimic other nail disorders such as onychomycosis or nail psoriasis. If not treated, it can eventually lead to permanent dystrophies in adulthood and *sequelae* related to feet malposition, like back pain. It is therefore crucial to examine the whole foot and recognize the toe position. Medical treatment is usually not necessary. Conservative measures are recommended, such as nail debridement or orthodigital devices. Referral to a podiatric practitioner is useful. Surgery is not recommended in children [67].

Onychotillomania and Onychophagia

Onychophagia affects all age groups but is more prevalent in children and adolescents, predisposing to psychosocial issues and complications including paronychia and dental problems. According to the study of Winebrake et al. including 281 patients, the prevalence of nail biting for more than 1 month was 37%, with a median age of onset of 5 years old. Only fingernails were involved in 88% of cases. There was a history of nail biting in 63% of cases. Biters were 3.34 times more likely to have a diagnosis of a psychiatric disorder than non-biters [68]. The study of Lynch et al. showed that children who suck their thumbs or bite their nails were less likely to have atopic sensitization in childhood and adulthood. On the contrary, no association was found with asthma or hay fever [69]. The application of bitter nail lacquers produced significant improvement in terms of odds of frequent nail biting [68]. Management of onychophagia includes a combination of pharmacotherapy, such as N-acetylcysteine and antidepressant therapy, stimulus control, habit reversal training, as well as cognitive behavioral and aversion therapy [68, 70]. N-Acetylcysteine warrants consideration as an efficacious pharmacological intervention due to its relative safety [68, 71]. Auricular acupressure appears to improve the efficacy of habit reversal treatment, likely by reducing anxiety [72]. Halteh et al. discourage practitioners to tell children that no treatment is needed and that they will outgrow it [73].

Retronychia

Retronychia is mostly described in adults, but pediatric cases have also been reported, with

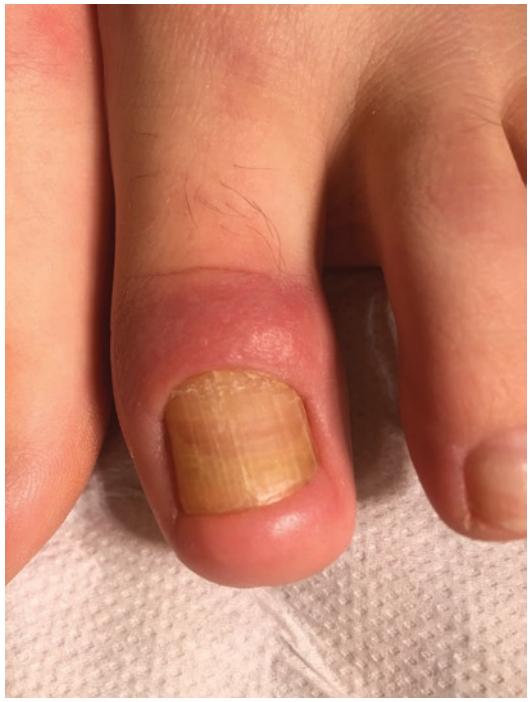

Fig. 14.6 Retronychia in a teenager

the same clinical features (Fig. 14.6) [74]. Until recently, nail avulsion was the treatment of choice. A study from Lencastre et al. evaluated the efficacy of potent topical steroids in retronychia. The youngest patient included in the study was 12 years old. Topical steroids were used under occlusion for an average duration of 8 weeks, with a complete or partial response in 41.1% and 28.5% of cases, respectively. Response correlated with milder paronychia and longer treatment durations. Topical steroids should therefore be the first-line treatment of retronychia, especially in milder forms, associated with shoewear and gait biomechanics assessment [75, 76]. Nail avulsion should still be performed if there is no improvement after 10 weeks [75].

Ingrown Nails

In the study of Arica et al., a positive family history of ingrown nail was present in 15.7% of patients. High prevalence of incorrect nail cutting (72.1%), trauma (36.1%), poorly fitting shoes (29%), hyperhidrosis (12.9%), and obesity (9.7%) were determined among the patients with ingrown toenails. The mean age at presentation was 15 years [77]. Ingrown toenails in children and adolescents should be treated in first instance by nonoperative methods, such as taping and nail brace application [78–80]. Operative options can be considered for resistant cases or in case of recurrence [80]. Partial nail avulsion with chemical matrix cauterization is considered as the technique of choice [81]. However, Livingston et al. suggested to consider the Vandenbos procedure – a large debulking of the lateral folds with secondary intention healing – which is associated with a low recurrence rate in children, adolescents, and young adults with ingrown toenails. Patient-reported recovery time, complication rate, functional outcomes, and satisfaction are excellent [82].

Key Points

- Fingertip injuries are common in children, mostly crushing by a door or a window. This should be preventable with adequate measures.
- Topical steroids are the first-line treatment of retronychia, especially in milder forms.
- Nail biting is common in children. It is associated with psychiatric disorders but reduces the risk of atopic sensitization.
- Ingrown toenails in children and adolescents should be first treated conservatively.

Nail Tumors

Subungual Exostosis

Subungual exostosis (SE) is an uncommon, benign osteocartilaginous tumor of the distal phalanx [83]. Half of the patients are under 18, with an equal female/male ratio [83–85]. The hallux is the most common location [83, 84].

Fingernails are rarely affected. Pain is a common complaint [83]. A history of trauma is present in about 30% of cases [84]. One study suggested that trauma, including surgeries, may have a dual function of induction and regression of SE [86]. Infections are also frequently implicated in the etiology of the disease [83]. A study focusing on dermoscopic features of subungual exostosis showed that vascular ectasia (Fig. 14.7) was the most common dermoscopic finding, followed by hyperkeratosis, onycholysis, and ulceration [87].

Longitudinal Melanonychia

The mean age at time of consultation for longitudinal melanonychia (LM) is 8 years old [6]. In a recent histopathological study of 30 childhood cases of melanonychia conducted in the USA, Cooper et al. reported subungual lentigo in 20 cases, subungual nevus in 5 cases, and atypical melanocytic hyperplasia in 5 cases [88, 89].

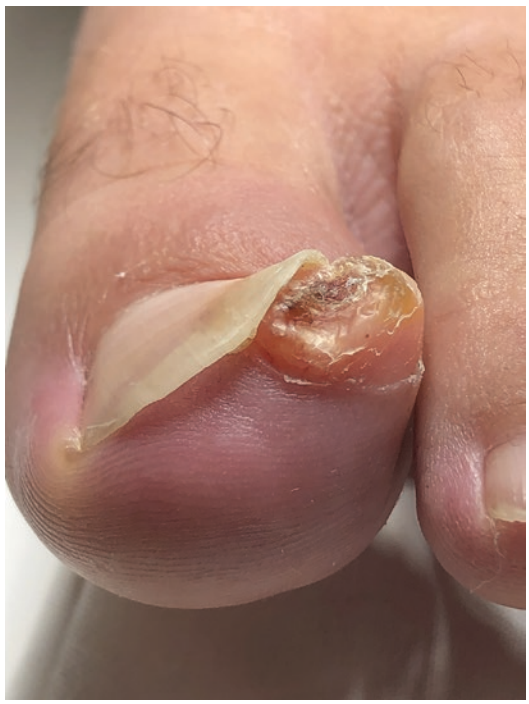

Fig. 14.7 Subungual exostosis of the hallux in a teenager

Childhood LM due to a benign nail matrix nevus (NMN) displays more melanoma-associated features compared with those of adults [90, 91]. Those features include a sharply demarcated pigment band of even width, a Hutchinson's sign – usually observed at the hyponychium and/or proximal nail fold cuticles – and a longitudinal brush pigmentation [91]. A pseudo-Hutchinson sign, a triangular sign, an irregular pattern, as well as dots and globules are also detected more commonly in children. NMN in children are darker and multicolored. Pigmentation also tends to be broader in children, but without statistical significance [90]. There is still no consensus on how to manage or follow up NMN in children. It has been shown that the predictive scoring model for dermoscopy of nail melanoma in situ couldn't be applied to the pediatric population (Fig. 14.8) [92–94]. Nail melanoma is exceedingly rare in children, with less than 20 cases of pediatric subungual melanoma in the literature, without any deaths reported to date [89, 92, 95]. Only two cases were subungual invasive melanomas that subsequently metastasized to regional lymph nodes without distant metastases, providing evidence that subungual melanoma with

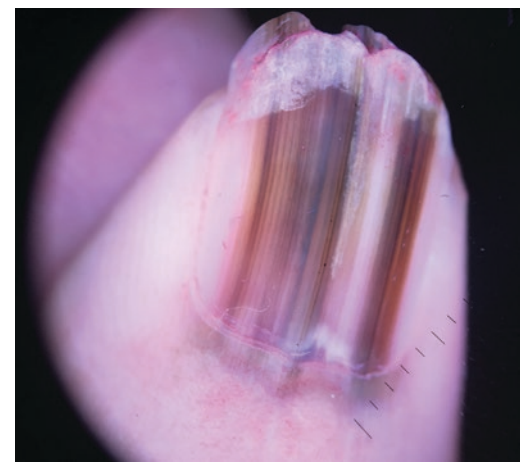

Fig. 14.8 Longitudinal melanonychia in a child. The dermoscopic aspect would be extremely worrying in an adult. These types of features are very common in LM in children and do not account at all for a malignant process. The lesion was removed after several years of follow-up and showed a junctional nevus

metastatic potential does occur in children, albeit exceptionally rarely [92]. Therefore, the vast majority of excised lesions are in fact benign, even if they display worrisome clinical, dermoscopic, or sometimes histopathological features [88, 96]. Considering the morbidity associated with surgical excision of the nail matrix and the rarity of nail unit melanoma in children, the overwhelming majority of cases can be managed conservatively with photographic and dermoscopic follow-up, especially under 14 years old, with biopsy only required in selected cases [88, 89, 92, 96]. When LM appears in older teenagers, a closer follow-up is required [89]. Piraccini et al. decide to biopsy only when the band rapidly enlarges and involves the whole nail and when its color is dark black. This management remains difficult, especially when dealing with anxious parents [94, 97].

Onychopapilloma

Onychopapilloma is a benign nail unit tumor that is usually seen in adults. Two cases of onychopapilloma in children – aged 9 and 10 years old – and one in a teenager have been recently described [98, 99].

Key Points

- Subungual exostosis affects mainly young patients; half of them are <18 years old.
- Longitudinal melanonychia is benign in children in the vast majority of cases, even if it frequently displays worrisome features. A wait-and-see policy is most of the time appropriate.
- Onychopapilloma is a benign longitudinal nail tumor which can occur in children and teenagers.

Systemic and/or Iatrogenic Disorders

Fever-Related Beau's Lines or Onychomadesis

A temporary cessation in matrix growth from a systemic shock like a thermal peak may result in a Beau's line or an onychomadesis, according to the duration of the injury [100]. This condition is observed mainly in the group 2 to 6 years old, most probably because of the fragile nail matrix in young children [6, 101]. Thirty percent of children with hand, foot and mouth disease (HFMD) have such nail abnormalities [102]. Fingernails are more commonly involved than toenails. Nail changes typically occur synchronously [101]. It is still debated whether the inhibition of the nail matrix proliferation results from direct inflammation spreading from skin lesions of HFMD around nails or a coxsackievirus-specific nail matrix involvement, or HFMD's severe systemic impact on the general condition of the small children [100]. In HMFD, nail changes usually occur within 1 or 2 months after onset and last for 1 to 8 weeks [101].

Yellow Nail Syndrome

YNS is a rare disorder and is even more rarely reported in children with around 20 cases described in the literature. As in adults, yellow nails and recurrent respiratory infections are the most common presentations. Lymphedema was also noted in 12 of 19 cases in the literature. There seem to be two age peaks in the incidence of YNS. Most pediatric cases presented at birth, maybe because of a transplacental crossing of titanium from the mother to the fetus. The second peak appears between the age of 6 and 10 and may be related to the high exposure to candy or children's toothpastes that contain titanium dioxide at this age. Avoiding titanium exposure could alleviate the symptoms of YNS [103]. The prognosis of YNS in children is not known [104].

Key Points

- Beau's lines and onychomadesis occur in 30% of children with hand, foot and mouth disease, within 2 months after the infection.
- Yellow nail syndrome is an extremely rare disorder in children, although severe. It may be related to titanium absorption from candies and toothpastes.

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15 Nail Changes with Targeted Antineoplastic Drugs

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The last two decades have been extremely productive in oncology pharmacotherapy resulting in an abundance mainly of targeted drugs. Until then, broad spectrum traditional antineoplastic drugs had been used but due to their unselective mechanism of action provoked a great range of undesirable effects. The targeted drugs can be classified according to their mechanism of action. They include proteasome inhibitors, toxic chimeric proteins, and signal transduction inhibitors such as tyrosine kinase (non-receptor and receptor), serine/threonine kinase, histone deacetylase, and mammalian target of rapamycin inhibitors. Increasingly used are also targeted vascular (VEGF) and platelet-derived endothelial growth factor blockade [1]. Despite their selective and precise mechanism of action, targeted therapies do not lack adverse effects (AEs). Cutaneous toxicities are among the most frequently observed AEs [2], and their prompt and adequate management requires a close collaboration of oncologists and dermatologists. Because they are often administered in long durations, preventive and therapeutic measures are more frequently needed than with conventional chemotherapies [3]. When referring to nail changes, it is important to remember that they represent past drug effects because of their slow rate of growth. Fingernails grow at 0.1 mm per day and toenails at 0.03 per month, requiring 4–6 and 12–18 months, respectively, to regrow. Thus, prevention of nail changes has to be practiced well before the onset of the first visible sign.

As demonstrated in various studies, nail changes are quite disturbing for cancer patients [4]. Broadly used grading systems of nail toxicity fail to demonstrate the range of nail alterations provoked by antineoplastic agents in general and their correlation with patients' quality of life.

Nail Toxicity Grading

The National Cancer Institute's Common Terminology Criteria for Adverse Events (NCICTCAE) categorizes a broad collection of AEs that are experienced by cancer patients during treatment, and each event has a structured description and rating of severity. The aim of each revision of the CTCAE is to include relevant treatment-related AEs and to update severity descriptions. The current version, v 5.0 (11/2017), divides nail AEs according to descriptive changes, namely, nail discoloration, loss, and ridging (Table 15.1). The severity of these AEs can be graded from mild to moderate given that they neither demand hospitalization nor threaten the patient's life [5].

Despite CTCAEs regular updates, another developed grading system seems to be even more

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Table 15.1 Common Terminology Criteria for Adverse Events (CTCAE) Version 5.0, section on nail changes

	Grade 1	Grade 2	Grade 3	Grade 4	Grade 5
Skin and Subcutaneous Tissue Disorders (CTCAE Term)					
Nail changes	Present				
Definition: A disorder characterized by a change in the nails					
Nail discoloration	Asymptomatic; clinical or diagnostic observations only				
Definition: A disorder characterized by a change in the color of the nail plate					
Nail loss	Asymptomatic separation of the nail bed from the nail plate or nail loss	Symptomatic separation of the nail bed from the nail plate or nail loss; limiting instrumental ADL			
Definition: A disorder characterized by loss of all or a portion of the nail					
Nail ridging	Asymptomatic; clinical or diagnostic observations only; intervention not indicated				
Definition: A disorder characterized by vertical or horizontal ridges on the nails					

precise when describing skin-related adverse events. EGFRIs are one of the best examples of skin-related toxicity at concentrations necessary for antitumor effects; the coincident inhibition of the EGFR in the skin and appendages results in altered keratinocyte function.

As the use of EGFRIs has been expanding in several solid tumors, the necessity of developing a better scale to fully characterize their toxicities in order to improve clinical research reporting, dosing adjustments during treatment, and management of treatment side effects was obvious. Thus, in 2010 the MASCC (Multinational Association of Supportive Care in Cancer) skin toxicity study group presented a new scale to detect and report EGFRI-related toxicities with greater sensitivity, specificity, and range than the scales currently used (MASCC EGFR Inhibitor Skin Toxicity Tool – MESTT) (Table 15.2). The severity grading (0–5) used was the same as in the CTCAE scale (Table 15.3). Concerning nail changes, this time they were divided according to the anatomical site of the nail apparatus affected, namely, changes of the nail fold, nail plate, and nail tip. Moreover, the severity grading reached grade 3 in all cases, and this is important because supportive care interventions and dose modifications usually take place in grades 3 and 4. This new scale could serve as an example for the future more adequate development of grading systems that could encompass the totality of skin-related adverse events due to targeted therapies [6].

Concerning the instrumental activities of daily living (iADL) where both scales rely on, there are typically eight areas of focus to assess how cancer therapy affects patients' activities: ability to use the telephone, laundry and dressing, shopping and running errands, transportation, meal preparation, medication management, housekeeping activities, and ability to manage finances. On the other hand, self-care ADL refers to bathing, dressing and undressing, feeding self,

Table 15.2 MASCC Study Group EGFRI-dermatologic AE grading scale, section on nail changes

Adverse event	Grade 1	Grade 2	Grade 3	Grade 4
Nail changes - nail plate	Onycholysis or ridging without pain	Onycholysis with mild/moderate pain; any nail plate lesion interfering with instrumental ADL	Nail plate changes interfering with self-care ADL	–
Nail changes - nail fold	Disruption or absence of cuticle; OR erythema	Erythematous/tender/painful; OR pyogenic granuloma; OR crusted lesions OR any fold lesion interfering on instrumental ADL	Periungual abscess: OR fold changes interfering with self-care ADL	–
Nail changes - digit tip	Xerosis and/or erythema without pain	Xerosis and/or erythema with mild/moderate pain or stinging; OR fingertip fissures; OR any digit tip lesion interfering with instrumental ADL	Digit tip lesions interfering with self-care ADL	–

Table 15.3 Common Terminology Criteria for Adverse Events (CTCAE) Version 5.0 – Grading

Grades	
Grade 1	Mild; asymptomatic or mild symptoms; clinical or diagnostic observations only; intervention not indicated
Grade 2	Moderate; minimal, local, or noninvasive intervention indicated; limiting age-appropriate instrumental ADL[a]
Grade 3	Severe or medically significant but not immediately life-threatening; hospitalization or prolongation of hospitalization indicated; disabling; limiting self-care ADL[b]
Grade 4	Life-threatening consequences; urgent intervention indicated
Grade 5	Death related to AE

Activities of daily living (ADL)

[a]Instrumental ADL refers to preparing meals, shopping for groceries or clothes, using the telephone, managing money, etc.

[b]Self-care ADL refers to bathing, dressing and undressing, feeding self, using the toilet, taking medications, and not bedridden

using the toilet, taking medications, and not confined to bed; that is why it is linked to a significantly deteriorated quality of life and a higher grading (grade 3) compared to iADL (grade 2) [7]. In the last years, a few attempts have been made to alter, improve, or completely change the current grading systems. A recently published article proposed the use of a novel scoring system for paronychia related to oncologic treatments (SPOT) and showed a good correlation of paronychia severity with DLQI and pain index. It may thus prove useful in clinical practice [8].

Nail Changes with Targeted Therapies

Table 15.4 illustrates the nail changes that result from targeted antineoplastic drugs.

Paronychia is the most frequent AE appearing on the nails of patients receiving targeted treatments. It is characterized by acute inflammation of the nail fold of one or more nails and presents as erythema, edema, and tenderness and may progress to painful pyogenic granuloma-like lesions, mimicking an ingrown nail. Pyogenic granuloma-like lesions result from the piercing of perionychium from the nail pate followed by an aberrant healing process and often appear at the proximal nail folds of the great toes. While initially sterile, superinfection of these lesions with bacteria, mainly *Staph. aureus* or fungi, may occur. If paronychia is painful, it may cause significant debilitation and result in substantial functional impairment thus leading to a reduction or cessation of treatment with the targeted therapy. Paronychia develops in 10–20% of patients treated with a first- or second-generation EGFR TKIs and occurs 20 days to 6 months after the start of treatment. It may also appear after treatment with mTOR, MEK, and BRAF inhibitors [3, 12, 32].

Onycholysis refers to the detachment of the nail plate from the nail bed and when caused by antineoplastic drugs is usually painful. Apart from the well-known taxane-induced phenomenon, it seems that, to a lesser extent, targeted therapies

Table 15.4 Nail changes with targeted antineoplastic drugs

Nail changes	Class of targeted antineoplastic drugs	References
Nail fold		
Paronychia/pyogenic granuloma-like lesions	EGFRi	[3, 9–15]
	MEKi	[16, 17]
	mTORi	[18, 19]
	BRAFi	[16, 20, 21]
Nail plate		
Onycholysis	EGFRi	[3, 22, 23]
	MEKi	[3, 16]
	mTORi	[19, 24]
Ridging/brittle nails	EGFRi	[3]
	MEKi	[16]
	mTORi	[19]
	Bruton TKI	[25]
Melanonychia	Imatinib	[26, 27]
Xanthonychia	mTORi	[28]
Nail bed		
Splinter subungual hemorrhages	VEGFR/VEGF	[3, 29]
	Cabozantinib	[30, 31]
Apparent leukonychia	TKI	[3]

such as EGFR, MEK, and mTOR inhibitors may also lead to onycholysis [3, 16, 19, 22–24].

Thinning of the nail plate, nail ridging, and brittle nails are all changes stemming from nail matrix affection by targeted drugs. EGFR, MEK, mTOR, and Bruton TK inhibitors may provoke such changes to the nail plate [3, 16, 19, 25].

Imatinib, a TKI, is known to induce transverse melanonychia, a rather rare AE of targeted therapies, whereas mTOR inhibitors may be responsible for another rare event, xanthonychia, i.e., yellow nail discoloration [26, 27].

Splinter subungual hemorrhages occur during the first weeks of treatment with VEGFRi and disappear spontaneously, growing out progressively with the nail. It seems that VEGFR inhibition restricts the physiological repair processes of the nail bed capillaries and might account for development of these lesions [3, 29–31].

Apparent leukonychia presents as parallel, white bands that disappear with pressure. It is probably caused by affected nail bed vessels and resolves after cessation of treatment [3].

Why Is It Important to Address Nail AEs?

Nail changes caused by antineoplastic drugs have to be properly addressed for multiple reasons. First of all they may significantly affect the quality of life of patients, including their physical, emotional, and psychological well-being, especially if they interfere with instrumental or self-care ADL. Additionally, paronychia when accompanied by bacterial or fungal infections in neutropenic patients, as they frequently are following antineoplastic treatments, may put their life at risk [32]. Furthermore, if the AEs are not timely addressed or prevented, they seem to augment significantly the cost of the patient's treatment. In a 2018 study, it was demonstrated that grade 1 dermatological toxicity does not require additional costs; however, the cost of treatment for grade 2 or 3 in the outpatient setting was about 185$/event, and hospitalization resulted in substantially higher costs (approximately $4500/event) [9]. Finally, nail AEs can

affect medication adherence and cancer therapy dosing, as adverse events of grade 3 or greater justify dose modifications [2].

Preemptive or Reactive Treatment?

In 2010 Lacouture et al. demonstrated the importance of preemptive treatment for skin toxicity in patients with metastatic colorectal cancer through the STEPP, phase II, open-label randomized trial. Patients receiving panitumumab-containing therapy were randomly assigned 1:1 to preemptive or reactive treatment. Preemptive treatment included use of skin moisturizers, sunscreen, topical steroid, and doxycycline. The incidence of specific > or = grade 2 skin toxicities during the 6-week skin treatment period was reduced by more than 50% in the preemptive group compared with the reactive group [33]. Patients in the preemptive group reported less QOL impairment than patients in the reactive group. In 2015 the J-STEPP phase III trial on the skin toxicity of panitumumab in Japanese patients with colorectal cancer yielded similar results. In the panitumumab-alone group, the cumulative incidence of ≥ grade 2 skin toxicities in 6 weeks was 28.1% in the preemptive group compared with 69.0% in the reactive group [34]. Preemptive treatment is currently recommended by most for all patients initiating treatment with anti-EGFR therapy and usually consists of oral antibiotics (doxycycline, minocycline) and topical corticosteroids, alone or in combination with daily nonpharmacological prophylactic measures, including moisturizers, sunscreen, and oatmeal baths. Preemptive daily treatment with corticosteroids has been shown to reduce the incidence of paronychia in both the J-STEPP and STEPP studies [9].

Preventive Measures

In order to minimize nail changes, patients are advised to follow preventive measures as long as they start treatment with a targeted antineoplastic agent. Careful nail inspection of the hands and feet should be repeated in every clinic visit. Patients are encouraged to keep their feet and hands as dry as possible and always use gloves when soaking their hands for a prolonged period of time. Their feet should be dried well before putting on shoes. Their nails should be regularly filed and clipped conservatively, and they should avoid frequent use of nail polish and nail polish removers. They also have to frequently moisturize their hands and feet using thick moisturizers or zinc oxide cream. Their shoes should be comfortable and flat so as to avoid friction and pressure of the toes. Finally they are advised to perform bleach soaks to prevent infection and take a supplement of biotin to strengthen their nails [14].

Treatments

In a retrospective study published in 2016, Goto et al. [35] evaluated all possible methods of treating cancer pharmacotherapy-induced paronychia in their clinic. The first-line treatment was strong corticosteroid ointment which in general was sufficient except for severe cases. Minocycline was another option for its anti-inflammatory and antibacterial properties but in their clinic did not result in significant improvement. Cryotherapy used for pyogenic granuloma-like lesions was not significantly effective as well; in some cases it even deteriorated pain and swelling. Adapalene [36] had been reported as effective due to its anti-inflammatory properties, but according to this study, it should be considered as a prophylactic or a combination treatment. Taping, i.e., separating the nail plate from the perionychium with a stretchable bandage, could be effective but is user-dependent and could be wrongly applied in cases of affected ADL. Chemical matricectomy with phenol 90% under local anesthesia appeared to be highly effective, providing additionally disinfecting and anesthetic effects. However, it

should be reserved for severe cases, when anticancer treatment is at risk because it is an invasive treatment, resulting to permanent partial nail loss. Apart from that, as long as anticancer therapy is not interrupted, paronychia and pyogenic granuloma-like lesions may recur. Other suggested treatments for paronychia are the use of gentamycin ointment for 4 to 5 weeks, use of topical calcineurin inhibitors, bathing the hands and/or feet in diluted chloramine bath daily in order to avoid superinfection, cushioning inserts within shoes to pad the affected nails, pain control, and daily application of platelet-rich plasma for paronychia [2]. Finally for the pyogenic granuloma-like lesions, agents with a drying effect such as topical silver nitrate and trichloroacetic acid may be beneficial [37] as well as the novel approach of topical b-blockers use. A recently published case series and review of the use of topical timolol 0,5% gel twice daily under occlusion for 30 days demonstrated at least partial benefit in the majority of treated patients and suggested this approach to fragile cancer patients unwilling to receive a more invasive treatment [38]. Other suggested treatment regimens were that of propranolol 1% cream once daily under occlusion and betaxolol 0.25% eye drops once daily under occlusion for 1 month accompanied by an excellent safety profile.

In case of onycholysis, the detached nail should be removed, the nail bed should be kept dry, and topical application of a steroid lotion for a few weeks is advisable. For brittle and fragile nails, nail lacquers that produce a barrier to the nail plate, such as hydroxypropyl chitosan or polyureaurethane 16%, seem to be useful [16, 39].

For the rest of the nail changes, there seem to be no effective treatments but the changes usually resolve after cessation of the responsible drug.

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Optical Coherence Tomography in Nail Research and Diagnosis

16

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Abbreviations

OCT	Optical coherence tomography
DLSO	Distal lateral subungual onychomycosis
D-OCT	Dynamic optical coherence tomography
MC	Myxoid cysts
NAPSI	Nail Psoriasis Severity Index
US	Ultrasonography

Background

Optical coherence tomography (OCT) is a noninvasive imaging tool enabling real-time imaging of skin, hair, and nails. It has also been widely investigated as a diagnostic tool in dermatology, particularly in non-melanoma skin cancer and inflammatory, bullous, nail, and hair diseases [1–3]. Nail disease diagnosis is based mainly on clinical examination, biopsies, and scrapings; however, noninvasive imaging technologies such as OCT may expedite diagnosis of pathologies in the nail unit [1, 4]. OCT is able to visualize the nail plate, bed, and matrix, as well as blood flow in nail bed [1, 3–5]. OCT provides clinicians with micrometer resolution images of morphological features of the nail and has been shown promising in exhibiting features characteristic of nail psoriasis, onychomycosis, nail hematoma, glomus tumor, and myxoid cysts.

Generally, OCT imaging is more accurate than existing ultrasonography and is approaching clinical utility much more rapidly. OCT images clearly provide more detail than a simple magnifying glass and are able to display both structural and functional aspects of the nail [5].

Technology

Optical Coherence Tomography

OCT is based on the principle of Michelson interferometry using infrared light (from an 830-nm superluminescence diode) to detect scattered light from target tissue and reconstruct the 2D/3D morphology [6]. The reflection of the light from tissue is measured and processed in order to improve the signal-to-noise ratio and transfer it to a computer-generated OCT image [7, 8]. As an imaging modality, it occupies a space between acoustic imaging and confocal microscopy in terms of its resolution and imaging depth, typically imaging to a depth of 0.4 to 2.00 mm with an optical resolution of 3 to 15 μm (Fig. 16.1).

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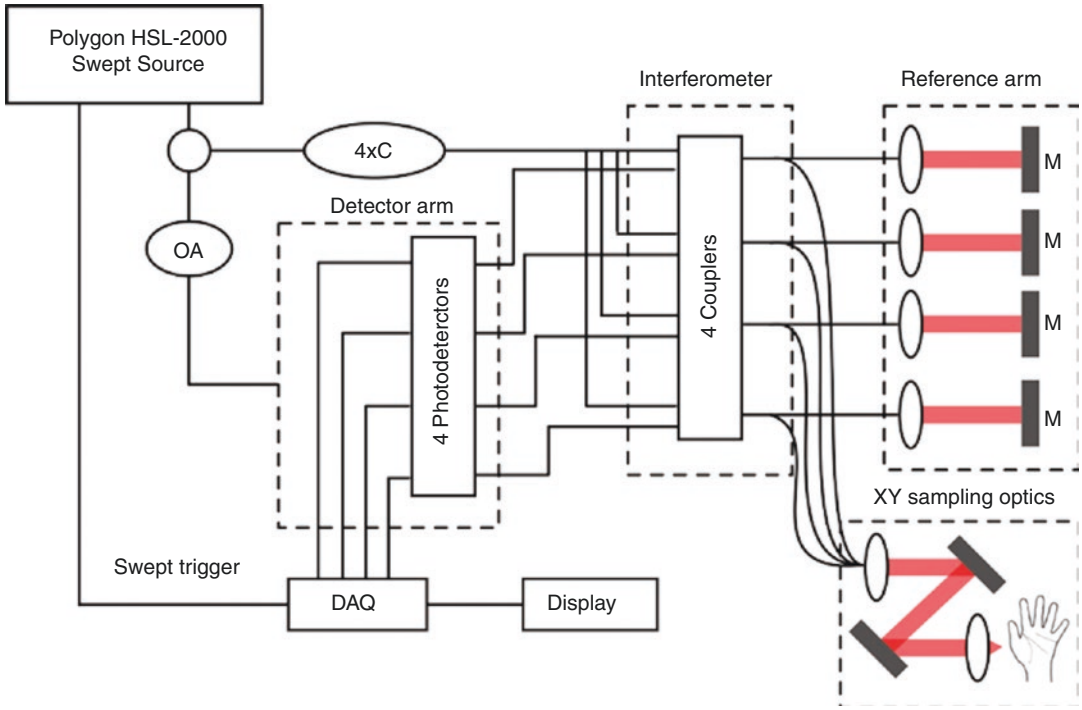

Fig. 16.1 Principle of optical coherence tomography. Schematic of multi-focus VivoSight optical coherence tomography. (Courtesy of Kamran Avanaki, PhD)

Dynamic Optical Coherence Tomography

A supplementary imaging technique, dynamic optical coherence tomography (D-OCT), allows the detection of vessels in transversal and en face/horizontal sections in real time to visualize the skin and nail bed microangiography [9–11]. D-OCT principles rely on detecting motion of blood cells during structural OCT scans by combining the image of the tissue structure with the blood vessel structures [9, 11].

Normal Nail

OCT visualizes images of the nail plate, the nail bed, and the matrix to a depth of 2 mm [4].

The nail plate is a modified form of stratum corneum, with a thick laminated keratinized structure overlying the nail bed and matrix. The nail plate is composed of 25 sheets of keratinized cells that can be divided into dorsal, intermediate, and ventral layers. Compared with the intermediate layer, the dorsal and ventral layers are thinner. The dorsal and ventral layers consist of harder skin-type keratin with lipids. In contrast, the intermediate layer is composed of hair-type keratin with few lipids, making the intermediate layer more flexible [12, 13]. OCT features of healthy nail plate are consistent with the above microscopic structure. The nail plate appears as a layered structure containing a varying number of horizontal homogeneous bands of varying intensity and thickness. The lunula contains distinct horizontal white band at the deep end of the nail plate. The nail bed is defined as the first change in OCT image intensity after the entrance signal, at the border of nail plate and nail bed (Fig. 16.2) [4].

Vascular changes coincide with structural features, nail fold, nail bed, and surrounding skin.

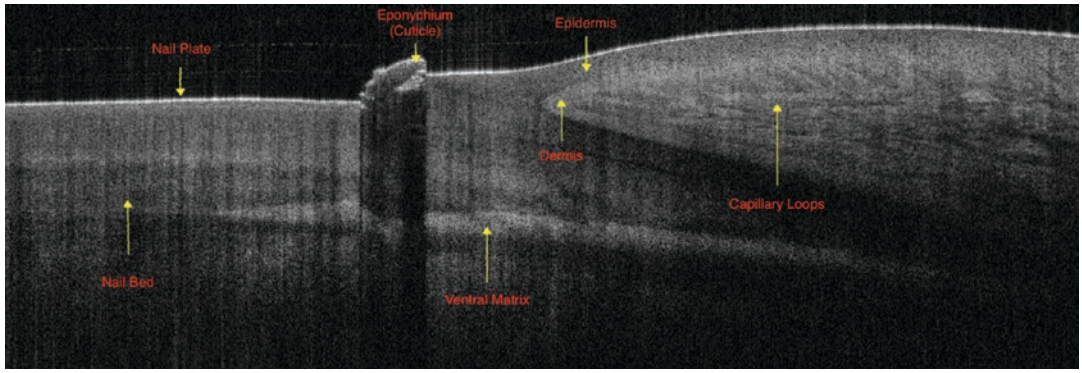

Fig. 16.2 Optical coherence tomography imaging of healthy nail and anatomic components of the normal nail unit. (Courtesy of Ali Rajabi-Estarabadi, MD, Department of Dermatology and Cutaneous Surgery, University of Miami Miller School of Medicine, Miami, FL, USA)

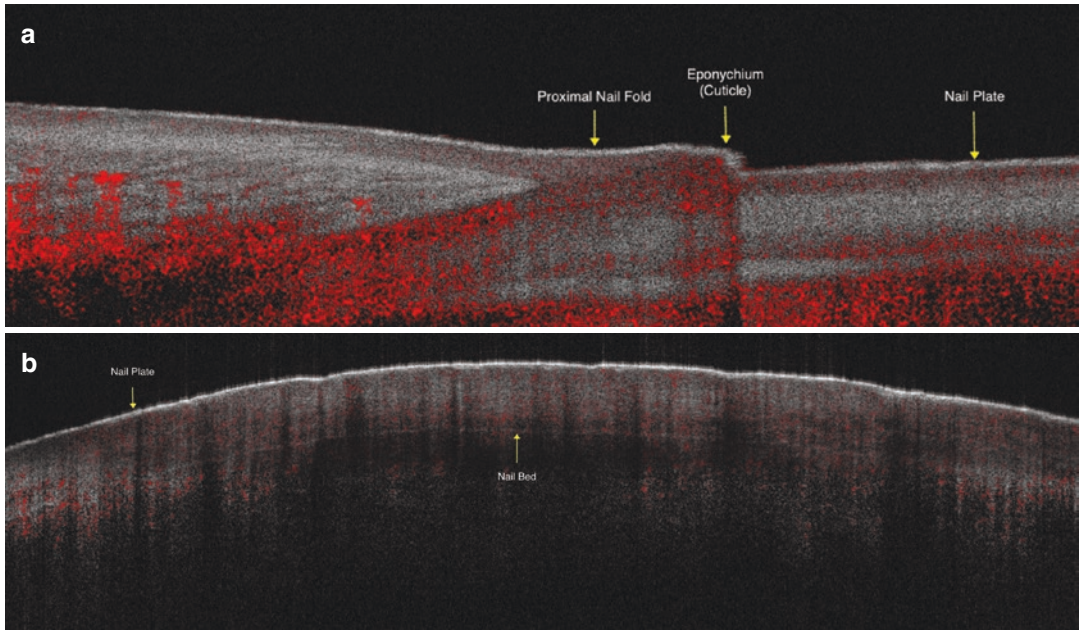

Fig. 16.3 Dynamic optical coherence tomography of healthy nail unit and vascular distribution at nail bed: (**a**) en face view, (**b**) trans-sectional view. (Courtesy of Ali Rajabi-Estarabadi, MD, Department of Dermatology and Cutaneous Surgery, University of Miami Miller School of Medicine, Miami, FL, USA)

The capillary loops of the proximal nail fold appear aligned compared to random distribution within the adjacent skin, and vessels in the nail bed appear more aligned along its leading edge. This is evidence that vascular traits and tissue structures are invariably linked [12] (Fig. 16.3).

Nail Psoriasis

Nail psoriasis most commonly involves the nail bed or nail matrix. Recently, the use of OCT has been incorporated in describing the characteristics of nail psoriasis. The first report on the

utility of OCT in nail psoriasis was in 2011 [7]. The researchers of this study not only described the morphological features of nail psoriasis on OCT imaging but also compared them to high-resolution ultrasonography (US). They found that OCT confirmed the ultrasonographic findings of a decreased trilaminar appearance of nails, which caused the nail plate to appear as one hyperechoic layer. However, OCT demonstrated higher resolution and specifically exhibited an inhomogeneous, eroded, and unevenly fused ventral plate.

The same authors subsequently studied 18 patients with at least 1 psoriatic nail compared to 12 healthy controls with both OCT and US. On OCT, leukonychia appeared as linear white stripes angled downwards in the proximal to distal direction [14]. Other white structures such as hyperreflective dots and thickening and irregularity of the superficial nail plate were also observed. These hyperreflective lesions on OCT demonstrated the highest sensitivity of all morphologic features mentioned (41.1%). Nail pitting correlated to small regions of sclerosis on OCT, which occasionally resulted in a shadow under the pit, whereas milder pitting demonstrated wavy abnormalities of the superficial nail. While the sensitivity of pitting and/or waving of the superficial layer was low (13.9%), the specificity was excellent (100%) (Fig. 16.4). Overall, the absolute agreement between OCT and clini-

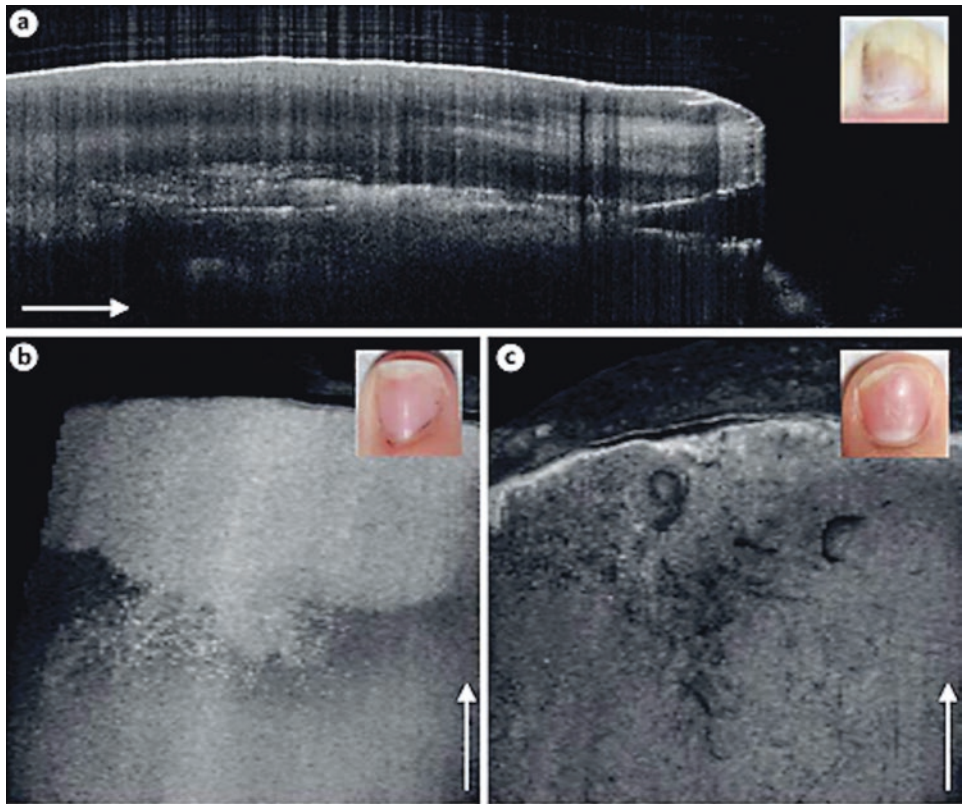

Fig. 16.4 Optical coherence tomography imaging of nail psoriasis vs healthy nail unit. Nail psoriasis: (**a**) Cross-sectional OCT image of a distal psoriatic nail: a wavy nail plate with white streaks and significant onycholysis overlying a highly reflective and irregular nail bed with white tufts. (**b**) En face view of a distal psoriatic nail demonstrating pronounced leukonychia and extensive speckling (depth 0.16 mm). (**c**) En face view of a distal psoriatic nail showing pitting (depth 0.30 mm). Healthy nail: (**d**) Cross-sectional view of a distal normal nail unit: a smooth nail surface, normal distribution of white speckles, and a linear regular nail bed proximal to the hyponychium. En face views at 0.16 mm (**e**) and 0.30 mm (**f**) in depth. (Reproduced with permission of [15])

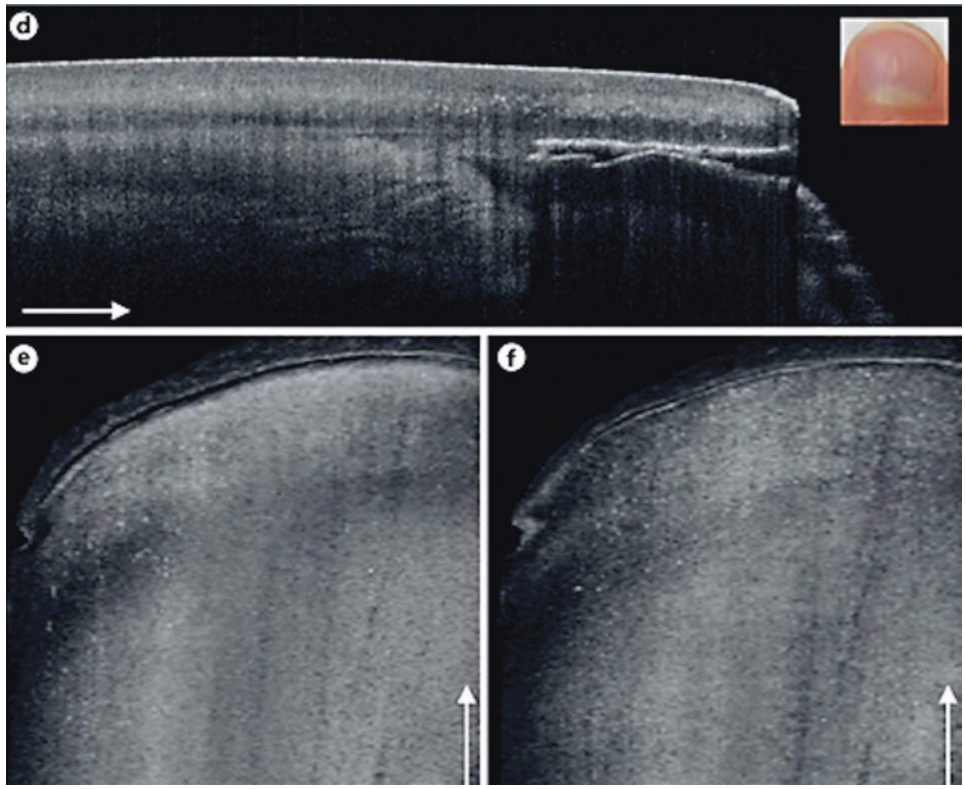

Fig. 16.4 (continued)

cal evaluation was 76.3% with a kappa value of 0.49 ($p < 0.0001$). OCT was able to identify abnormalities in 12 of 58 clinically normal nails in psoriatic patients compared to 5 of 120 nails of healthy controls. This suggests that OCT is able to detect subclinical nail involvement and may thereby have a role in identifying patients without obvious psoriatic lesions.

Furthermore, the specific vascular features of nail psoriasis have also been investigated using OCT. In a study of 16 psoriatic nails and 16 control nails, psoriatic nails exhibited significantly more blood flow at the proximal nail plate despite an increased nail thickness [15]. Psoriatic nails were also more likely to display dilated vessels with a haphazard architecture at the proximal nail fold (Fig. 16.5).

Other studies have highlighted the utility of OCT in assessing the therapeutic response of various treatments for nail psoriasis. Currently, the Nail Psoriasis Severity Index (NAPSI) is the most commonly used method of evaluating psoriatic nails and response to treatment. However, this tool is relatively subjective. Abignano and colleagues evaluated OCT changes occurring in 40 psoriatic fingernails before and after a 6-month treatment with apremilast [16]. The researchers developed a scoring system with OCT that included the presence or absence of leukonychia, pitting, diffuse surface waving, onycholysis, and subungual hyperkeratosis. Concurrently, a dermatologist blinded to these findings provided a NAPSI score for each nail. In general, the authors found that OCT identified more baseline abnormalities in nails than the clinical tool was able to detect. However, the outcomes of the clinical and imaging assessments were consistent in demonstrating improvement or worsening of nail psoriasis. The only exceptions were two cases where OCT demonstrated improvement in nails marked as "stable" by NAPSI and three cases where OCT found mild irregularities in nails marked as "normalized" by NAPSI.

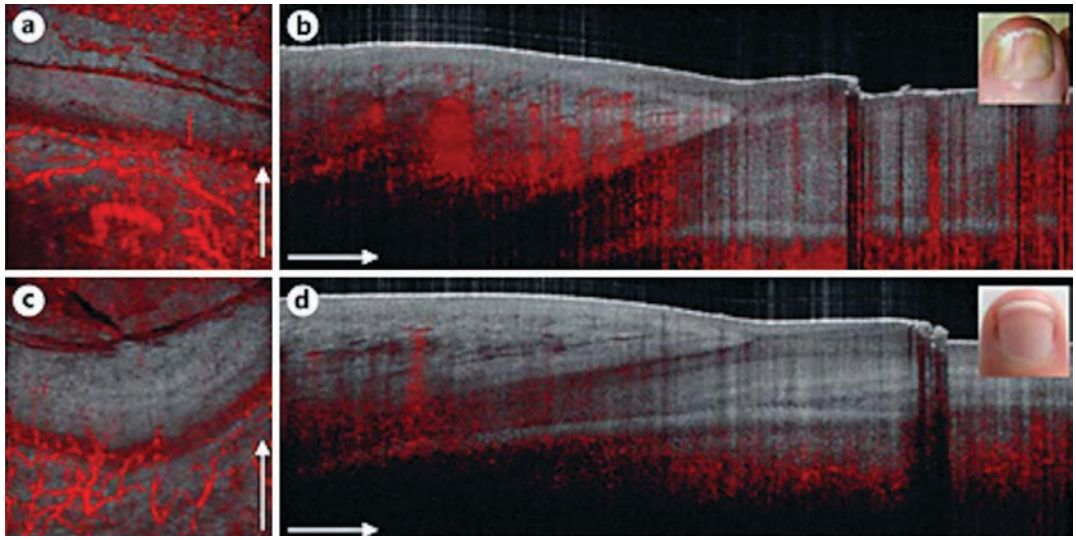

Fig. 16.5 Dynamic optical coherence tomography (D-OCT) of nail psoriasis vs healthy nail unit. Vascular features of nail psoriasis in the proximal nail fold: (**a**) En face view of a psoriatic nail: dilated vessels in a haphazard orientation (depth 0.6 mm). (**b**) Cross-sectional view: an increased density of blood vessels protruding superficially. Vascular features of healthy nail: (**c**) En face view of a healthy nail (depth 0.6 mm). (**d**) Cross-sectional view of the same healthy nail. (Reproduced with permission of [15])

Overall, these studies suggest that OCT may provide a more objective, quantitative, and structure-specific evaluation of nail psoriasis than pre-existing clinical tools. The clinical use of OCT may have prognostic potential as well, such as whether subclinical nail disease detected on OCT may predict arthritis. Ultimately, prospective studies with larger numbers are needed to clarify its potential role as a marker for nail psoriasis.

Onychomycosis

Onychomycosis occurs when a nail is infected with a fungal organism, most commonly dermatophytes such as *Trichophyton rubrum*, but can also occur secondary to yeast and non-dermatophyte molds. While a KOH preparation is the preferred initial test for suspected onychomycosis, OCT has recently demonstrated promise as a method of confirmation. As onychomycosis is the most common nail disorder seen in clinical practice, the application of OCT for this condition has been studied relatively more than for other nail disorders. Studies incorporating OCT have described the morphological characteristics of onychomycosis and have demonstrated the utility of this tool in increasing the diagnostic sensitivity.

A classic finding of onychomycosis is thickening of the nail plate, which can be visualized on OCT. This thickening is due to reactive subungual hyperkeratosis of the infected nail. OCT may also demonstrate a decrease in differentiation of scattering parallel layers of the nail plate [17]. Fungal elements typically appear as elongated, high-scattering structures, representing groups of hyphae, surrounded by low-scattering areas, correlating to the lacunas of the hyperkeratotic nail plate. This pattern is due to the high chitin concentration of fungal elements, which reflect more light and thus generate a higher signal intensity on OCT than the surrounding regions. Other reports describe fungal elements as white lengthy or thready structures or round aggregated white structures [18]. In addition to the presence of hyperreflective lines, hyperreflective dots, and irregular surfaces, more recent studies suggest that the morphologic features of onychomycosis on OCT can be further subdivided per clinical subtypes. For example, it has been reported that onychomycosis presents with diffusely demar-

cated lines rather than sharply demarcated lines and tends to lack surface irregularity [5]. In addition, distal lateral subungual onychomycosis (DLSO) commonly portrays hyperreflective dots. In a series that included 12 cases of onychomycosis demonstrating hyperreflective dots, DLSO was the only clinical subtype to specifically display clustered dots [5]. The authors of this series postulated that clustered dots may represent a proximal spread of infection, as the hyphae are not condensed to the point of forming clear-cut lines. More specifically, OCT has also been utilized to visualize complications of onychomycosis, such as dermatophytoma. A dermatophytoma is a thick, localized area of infection in the nail plate that is composed of dermatophytes compacted into a fungal ball. In a series of six cases, it was found that dermatophytomas typically appear as well-demarcated avascular masses with jagged borders, located above the vascular nail bed and below a disorganized nail plate [2] (Fig. 16.6).

While the terminology and diagnostic criteria for OCT in onychomycosis are still being developed, studies suggest that the above morphologic features may assist in increasing the sensitivity of diagnosis. In a pilot study of ten patients with histologically proven onychomycosis, OCT demonstrated fungal elements in all patients [17]. In contrast, KOH preparations and fungal cultures revealed positive results in only five and six patients of the ten patients, respectively. These results indicate that OCT is a reliable method of diagnosing onychomycosis, even in cases of false-negative KOH preparations and cultures. In contrast, Rothmund and colleagues determined OCT to be ineffective in diagnosing onychomycosis due to a high number of false-positive results. They found that the specificity of diagnosing onychomycosis with OCT was lower than KOH preparation, culture, PAS staining, PCR, and confocal laser scanning microscopy. The researchers attributed the poor specificity to the low resolution of the machine, which did not allow for precise differentiation of hyphae and other nail structures, as well as possible artifacts that may appear similarly. Although the specificity of OCT was not impressive in this study, the authors found that its sensitivity was second best to PCR (94.9% vs 92.3%).

Furthermore, understanding the characteristics of onychomycosis on OCT may aid in obtaining optimal nail scrapings. Olsen and colleagues recommend that areas appearing as dark bands on OCT should not be targets of nail scrapings, as these low-scattering regions generally represent lacunae and not fungal elements [5]. Using OCT as an adjunct may thereby increase the sensitivity of nail scrapings. In addition, OCT may serve useful in determining whether a mycotic

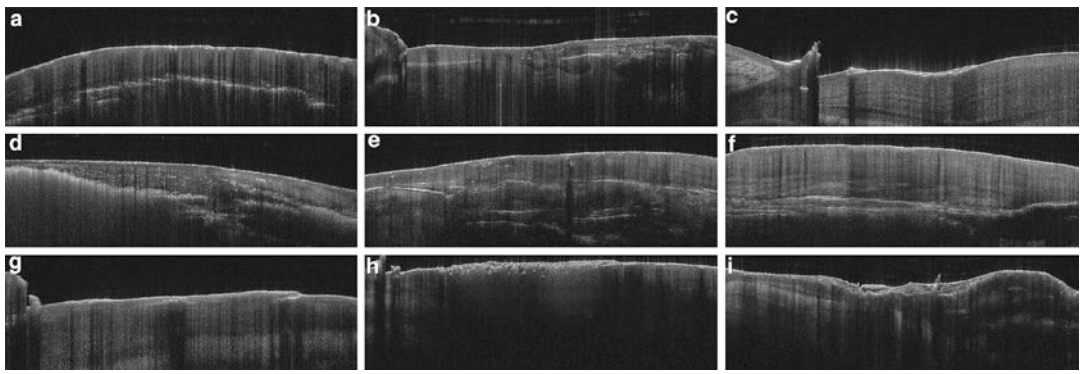

Fig. 16.6 Optical coherence tomography feature of onychomycosis. Cross-sectional view of proximal nail: (**a**) Sharply demarcated hyperreflective lines. (**b**) Clustered hyperreflective dots. (**c**) Dark band and a mildly irregular surface. (**h**) Moderately irregular surface. (**g**) Mildly irregular surface. Cross-sectional view of distal nail: (**d**) Diffusely demarcated hyperreflective lines and clustered hyperreflective dots. (**e**) Singular hyperreflective dots and sharply demarcated hyperreflective lines. (**f**) Disturbed architecture and sharply demarcated hyperreflective lines. (**i**) Severely irregular surface. (Reproduced with permission of [5])

cure has been accomplished. Some reports have even highlighted the use of OCT specifically for performing and monitoring laser treatment for onychomycoses [19]. Overall, while the use of OCT in this disorder is still relatively new with questionable specificity, its potential role in the management of onychomycosis is wide-ranging, spanning from diagnosis to therapeutic monitoring.

Subungual Myxoid Cysts

Myxoid cysts (MCs) of digits generally present as firm, translucent nodules arising from the dorsum of the digit and located between the crease of the distal interphalangeal joint and the proximal nail fold. De Berker classified MCs into three subtypes based on the location of the lesions: (a) located on the dorsum of the digit and between the crease of the distal interphalangeal joint and the proximal nail fold, (b) located beneath the proximal nail fold, and (c) extending beneath the nail matrix.

Type B and C create a space-occupying lesion that can affect microvasculature, nail matrix function, and nail shape and integrity. A longitudinal groove in the nail plate can be seen in MCs located distal or beneath the nail fold. Subungual MCs are more difficult to recognize than the more superficial variety, and the characteristic mucoid discharge is rare in this location [20].

OCT imaging of subungual MCs can demonstrate nail changes including cystic lesions beneath the nail (represented by hypointense areas), alteration in blood flow due to local pressure of the space-occupying cystic lesions, and a disorganized nail plate (Figs. 16.7 and 16.8).

Onychomatricoma

Baran and Kint first described onychomatricoma in 1992 [21]. Onychomatricoma is a rare, benign, slow-growing, and painless neoplasm of the nail matrix that clinically presents as a longitudinal whitish or yellowish band (longitudinal leuk-

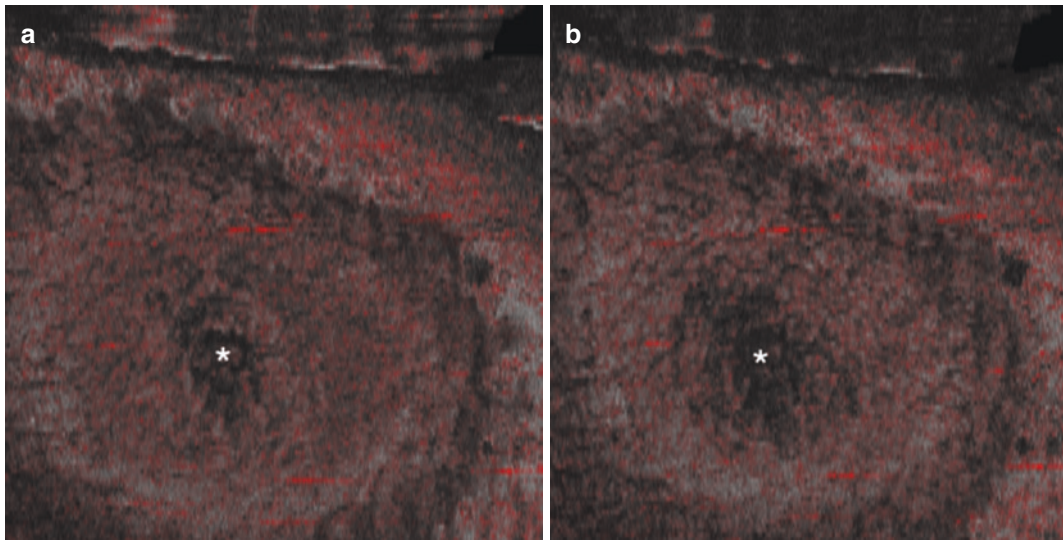

Fig. 16.7 OCT en face view of subungual myxoid cysts: well-circumscribed, oval-shaped soft tissue mass with peripheral rim enhancement, central enhancement, and lack of internal vascularity. Central hypointense area suggests fluid accumulation inside the surrounding tissue at different depths (**a**: 0.25 mm, **b**: 0.30 mm, **c**: 0.35 mm, **d**: 0.40 mm, **e**: 0.45 mm, and **f**: 0.50 mm). (Courtesy of Antonella Tosti, MD, and Ali Rajabi-Estarabadi, MD, Department of Dermatology and Cutaneous Surgery, University of Miami Miller School of Medicine, Miami, FL, USA)

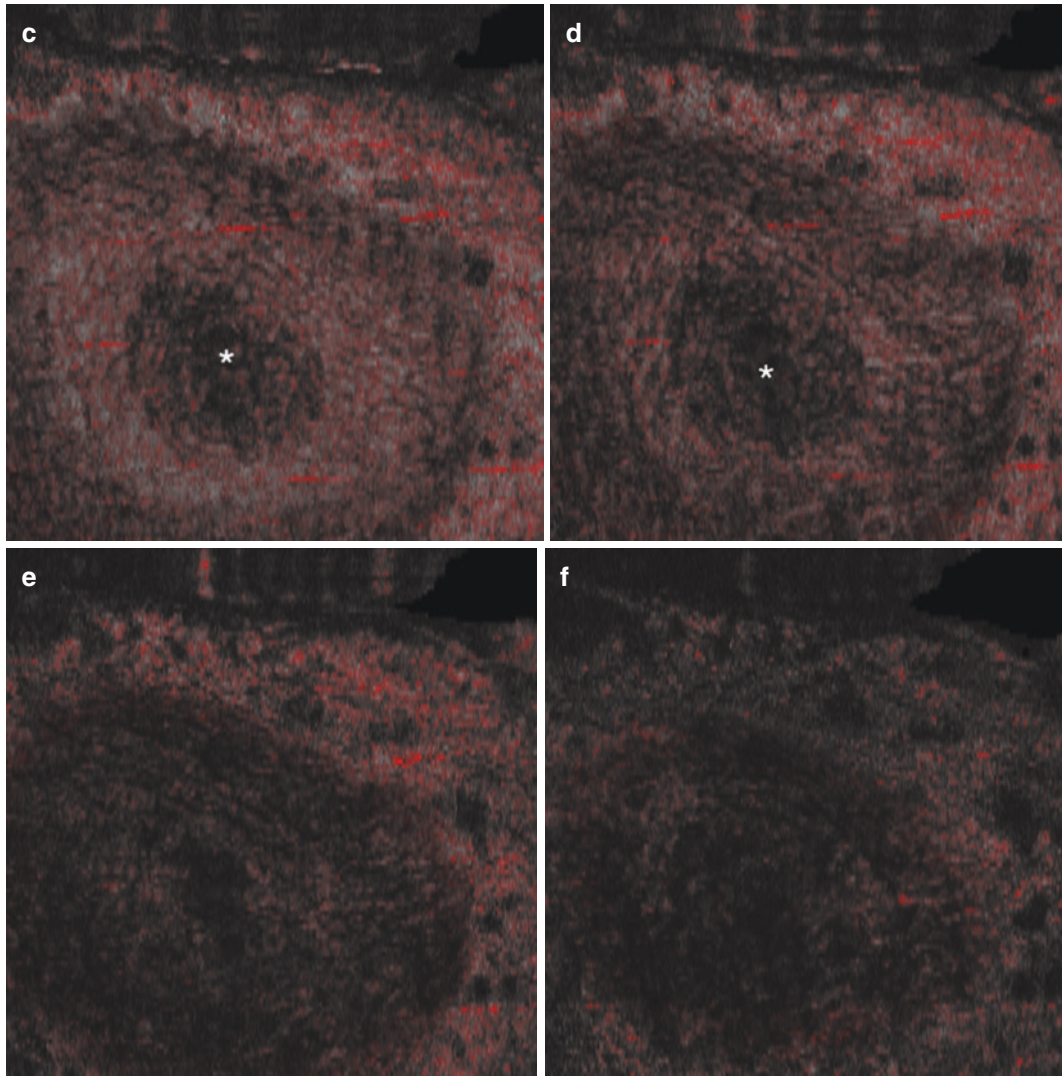

Fig. 16.7 (continued)

onychia or xantonychia) with a thickened nail plate and splinter hemorrhages at the proximal end [22, 23]. Cinotti et al. described OCT features of onychomatricoma in 2018. OCT visualized the tumoral cavities as multiple hypointensive oval-shaped cavities inside the nail plate with curvature of the nail plate [22]. D-OCT also can visualize splinter hemorrhages in the proximal part of the nail (Fig. 16.9).

Glomus Tumor

Glomus tumors are painful, benign perivascular neoplasms of the glomus body. The glomus body is a perivascular temperature-regulating structure consisting of an afferent arteriole, anastomotic vessel, primary collecting vein, intraglomerular reticulum, and a capsular portion. It is located in the stratum reticularis of the

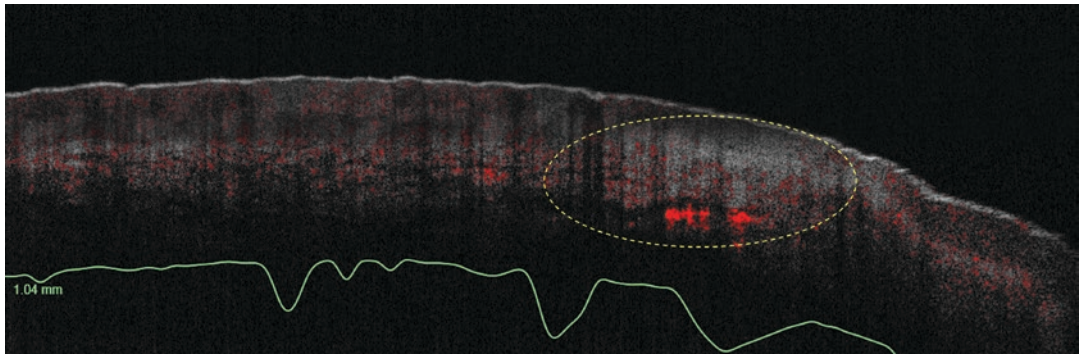

Fig. 16.8 OCT cross-sectional view of subungual myxoid cysts – space-occupying lesion with uniform enhanced density and increased peripheral blood flow. (Courtesy of Antonella Tosti, MD, and Ali Rajabi-Estarabadi, MD, Department of Dermatology and Cutaneous Surgery, University of Miami Miller School of Medicine, Miami, FL, USA)

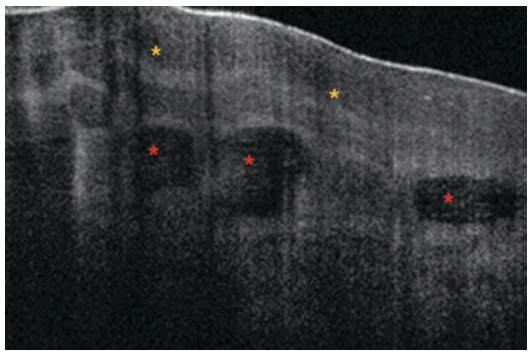

Fig. 16.9 Onychomatricoma: optical coherence tomography of the free edge of a nail shows multiple hypointensive oval-shaped cavities inside the nail plate (red asterisk) with curvature of the nail plate cavities inside the nail plate (yellow asterisk). (Reproduced with permission of [22])

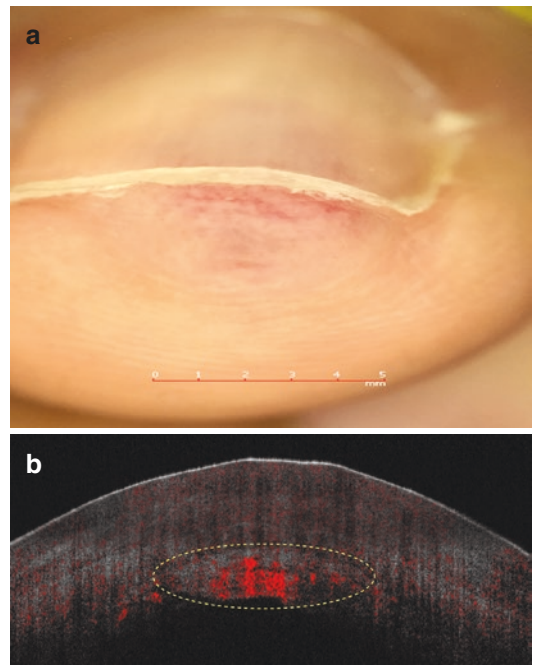

Fig. 16.10 Glomus tumor. (**a**) Dermatoscopy. (**b**) OCT cross-sectional view: vascular oval-shaped mass with a significant increase in blood flow, consistent with the angiomatous subtype of the glomus tumor. (Courtesy of Antonella Tosti, MD, and Ali Rajabi-Estarabadi, MD, Department of Dermatology and Cutaneous Surgery, University of Miami Miller School of Medicine, Miami, FL, USA)

dermis [1]. *Masson* et al. defined four histological types of glomus tumors: (I) an angiomatous form, (II) one with fewer vessels and a larger proportion of Musculoendothelial stroma, (III) one composed largely of nerve fibers, and (IV) a degenerative form showing either edema or hyaline and mucoid changes [24].

D-OCT is well-suited as an outpatient diagnostic imaging modality for glomus tumors and may help distinguish angiomatous subtypes from less vascular tumors (*Masson* subtype 2). In 2019, Rajabi-Estarabadi et al. described the OCT features of glomus tumors. OCT demonstrated destruction of the lunula (by mass effect) and longitudinal ridging. In two cases, dynamic blood flow evaluation revealed a vascular tumor with a significant increase in blood flow, consistent with the angiomatous subtype of the glomus tumor (Fig. 16.10) [1].

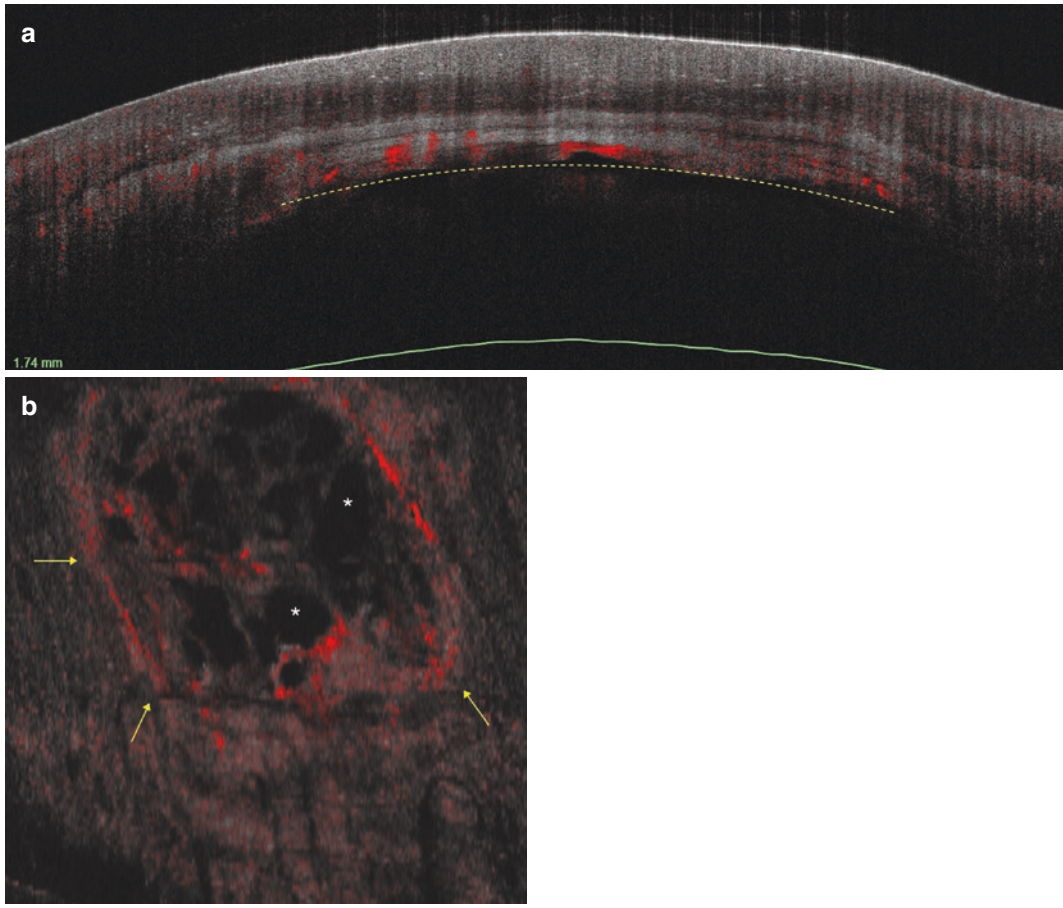

Fig. 16.11 Glomus tumor. (**a**) Cross-sectional view: area of hyperreflective with minimal tumoral core vascularity and increased peripheral vascularity. (**b**) En face view of the same lesion with minimal vascular flow and larger proportion of musculoendothehal stroma, representing Masson histopathological subtype II. (Courtesy of Antonella Tosti, MD, and Ali Rajabi-Estarabadi, MD, Department of Dermatology and Cutaneous Surgery, University of Miami Miller School of Medicine, Miami, FL, USA)

Additionally, it can be presented with ovoid area of hypointensity with minimal tumoral core vascularity and increased peripheral vascularity in OCT imaging which is representing *Masson* histopathological subtype II (Fig. 16.11) [1].

Summary

OCT effectively complements other imaging modalities by visualizing blood flow and providing images with a sufficient depth and a high resolution. OCT enables fast detection of specific vascular features of nail psoriasis and subclinical morphologic nail changes. OCT is a reliable diagnostic method in onychomycosis, even in cases of false-negative KOH preparations and cultures. The use of OCT may be helpful in avoiding multiple biopsies and can measure the therapeutic efficacies in the treatment of several nail disorders such as nail psoriasis and onychomycosis. D-OCT offers distinct advantages in imaging nail diseases and can aid in the differentiation of various subtypes of glomus tumors. Overall, OCT is a remarkable addition to other imaging techniques in dermatology and offers a noninvasive, high-resolution diagnostic approach.

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Drug-Induced Nail Changes

17

Uwe Wollina

Introduction

Nails are the largest and most complex specific product of skin. The nail of the middle finger of the dominant hand has a growth rate of approximately 0.1 mm/day, whereas the big toe nail grows slower, i.e., 0.03–0.05 mm/day [1]. The nail is also a target for treatment, and transungual drug delivery is primarily used to combat onychomycosis [2].

The nail plate is a continuously growing structure composed of keratin, water, minerals, and cholesterol. Both nail matrix and proximal nail bed contribute to nail plate formation. Nail bed, nail folds, cuticle, and distal groove complete the nail organ, and all may be affected by adverse drug reactions [3]. The use of medical drugs may interfere with the normal growth and maturation of nails leading to characteristic clinical symptoms. This review will focus on adverse events of medical drug therapy on nail growth, structure, and coloration.

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Diagnostics of Drug-Induced Nail Changes

The detailed medical history is essential for diagnosis. In contrast to drug-induced skin and hair changes, nail changes develop slower and with a delay often of several weeks. There can be a time gap between symptoms on fingernails and toenails of 2 to 3 months due to the different growth rates. In case of color changes, a nail plate biopsy is helpful to differentiate between subungual bleeding and melanin. Changes of nail plate structure need a differentiation into occupational and infectious causes including mycology. Other laboratory investigations are rarely necessary [3].

Chronic Paronychia

Paronychia is a painful inflammation of the fingers or toes in one or more of the three nail folds and can be differentiated into acute and chronic subtypes. Acute paronychia is caused by multimicrobial infections after the protective nail barrier has been breached. Chronic paronychia is defined as a disease with ≥6 weeks of duration, and it can be caused by occupational factors like wet work or by medical drugs [4].

Retinoids (vitamin A and its metabolites) are potent natural regulators of cellular activities, including cell growth and differentiation. Biologically active retinoids exert their effects

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https://doi.org/10.1007/978-3-030-59997-3_17

by binding to nuclear retinoic acid receptors and retinoid X receptors. The group of pharmacologically used retinoids include naturally occurring and chemically synthesized vitamin A derivatives [5]. Systemic retinoids can cause dry skin and chronic paronychia. The nail fold affection has been observed more common in patient with acne and isotretinoin treatment and in patients with psoriasis and etretinate medication [6, 7] (Fig. 17.1). Acitretin is much less toxic to the nail than etretinate [8].

Paronychia is a common cutaneous toxicity during treatment with epidermal growth factor receptor inhibitors. It has been observed in about 10% of patients receiving cetuximab and 25% of patients receiving panitumumab [9, 10] (Fig. 17.2). Even more common is chronic paronychia with epidermal growth factor receptor tyrosine kinase inhibitors such as gefitinib or erlotinib. With these medications, chronic paronychia occurs in up to 22% (gefitinib) and up to 40% (erlotinib), respectively [8, 11], and is independent from the drug concentrations in the affected finger or toe tips [12]. Lung cancer patients treated with osimertinib develop paronychia in 49.4% [13].

Other drugs related to chronic paronychia are vascular endothelial growth factor inhibitor bevacizumab [8], MEK inhibitor selumetinib [14], and B-rapidly accelerated fibrosarcoma (BRAF) inhibitor vemurafenib [15]. BRAF inhibitor encorafenib is not known to induce nail changes [16]. Renal cancer patients treated with mammalian target of rapamycin (mTOR) inhibitors develop paronychia in 22.2% [17].

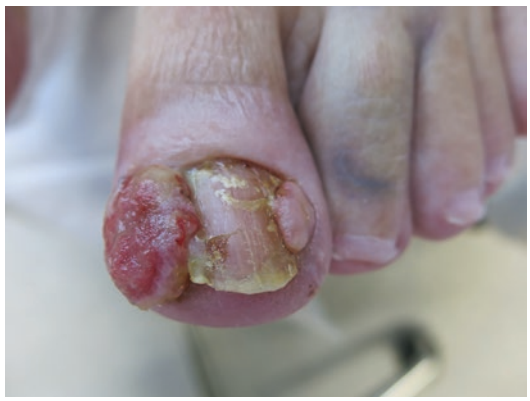

Fig. 17.1 Chronic paronychia of toenails induced by etretinate

Periungual and Subungual Pyogenic Granuloma

Pyogenic or telangiectatic periungual granuloma is a benign lobular capillary hemangioma of skin and mucous membranes. PG can arise spontaneously, in sites of injury, or within capillary malformations [18]. Multiple periungual tumors have been reported in rituximab-treated rheumatoid arthritis [19]. Acitretin and imatinib can cause pyogenic periungual granuloma [8] (Fig. 17.3). Subungual and periungual pyogenic granuloma have been reported in breast cancer patients treated with paclitaxel [20].

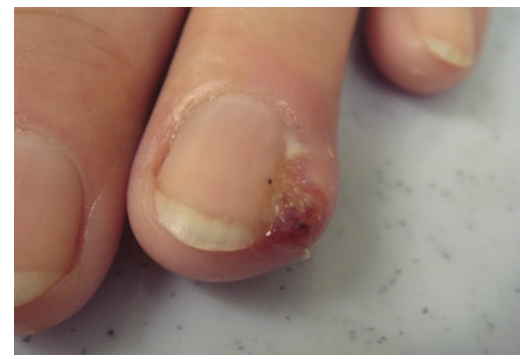

Fig. 17.2 Fingernail paronychia in a lung cancer patient treated with panitumumab

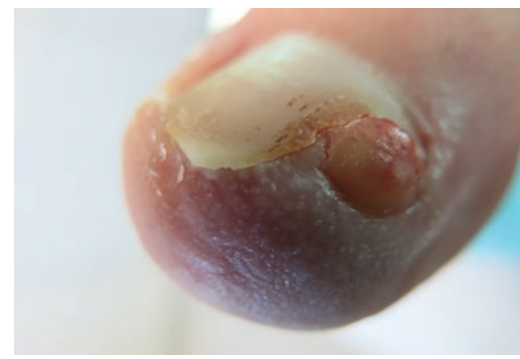

Fig. 17.3 Acitretin-induced periungual pyogenic granuloma

Drug-Induced Onycholysis

Capecitabine is a cancer drug that is known for onycholysis [21]. Polychemotherapy bears a higher risk for this adverse event. In patients with prostate cancer treated by sequential mitoxantrone/prednisone and docetaxel/estramustine, onycholysis was one of the most frequent non-hematological toxic effects [22].

Taxane-based therapy can be responsible for the periarticular thenar erythema with onycholysis (PATEO) syndrome. It has been suggested that taxanes activate neurogenic inflammation by prostaglandin release from nociceptive C-fibers [23].

A closely related disease is the asymmetric acral spared phenomenon, which has been observed during treatment with adriamycin, multikinase inhibitor sorafenib, or paclitaxel [24].

Intoxications may induce onycholysis, such as mercury or dioxin (Fig. 17.4) [25]. Another important differential diagnosis is onychomycosis [3].

Drug-Induced Photo-Onycholysis

Drug-induced photosensitivity is the result of interaction between a chemical agent and sunlight. Photosensitivity reactions can be classified as phototoxic or photoallergic. Sometimes, there is an overlap between these two patterns. The main topical agents that cause contact photosensitivity are the nonsteroidal anti-inflammatory drugs, whereas the main systemic drugs inducing photosensitivity are antimicrobials, nonsteroidal anti-inflammatory agents, and cardiovascular drugs [26, 27].

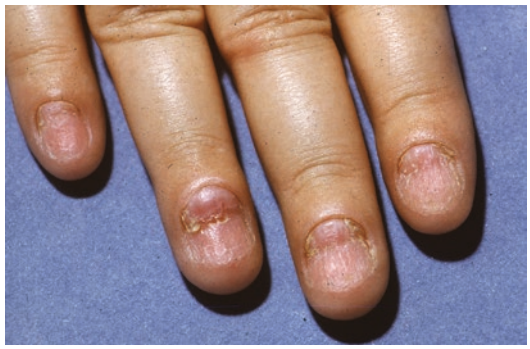

Fig. 17.4 Onycholysis after mercury intoxication

Table 17.1 Classification of photo-onycholysis according to Baran and Juhlin (1987) and Baran et al. (2019)

Type	Characteristics
I	Half-moon-shaped onycholysis, distally concave shaped
II	Circular notch opened distally, shaped as if the distal nail plate acted as a convex lens
III	Onycholysis in the central part of the nail plate only
IV	Blisters under the nail plate

Nail photo-onycholysis is a peculiar photosensitivity of the nail organ. Nail photo-onycholysis has been differentiated into four subtypes (Table 17.1) [28, 29]. While classical tetracyclines are well-known for phototoxicities, doxycycline has only rarely been identified as a cause of photo-onycholysis [29, 30]. Other antimicrobials responsible for photo-onycholysis include chloramphenicol, fluoroquinolones (moxifloxacin, ofloxacin), cephaloridine, and cloxacillin [31].

Taxanes increase the risk of phototoxicities [32] (Fig. 17.5). Other anticancer drugs that can cause such adverse events include vemurafenib, vandetanib, or epothilone [29]. In rare cases, immunosuppressant sirolimus can cause photo-onycholysis [33]. Nonsteroidal anti-inflammatory drugs such as diclofenac, benoxaprofen, and indomethacin, antifungals like griseofulvin and voriconazole, and antipsychotics (stanzapine, chlorpromazine, aripiprazole), oral contraceptives, thiazide diuretics, psoralens, and photosensitizers (aminolevulinic acid, methyllevulinic acid) are potential causes of photo-onycholysis [29, 34].

Nail Pigmentations

Melanonychia is a brownish or blackish nail plate coloration either of the whole plate or in a streaked pattern. In the differential diagnosis, melanocytic nevi, subungual melanoma, and subungual hematoma should be excluded. However, several drugs are known to cause melanonychia as well (Table 17.2) [35].

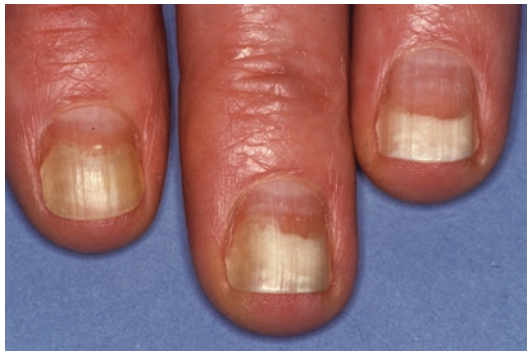

Fig. 17.5 Type I photo-onycholysis induced by docetaxel

Table 17.2 Drug-induced melanonychia – a selection

Drug	Remarks
Adriamycin	With hyperpigmentation of skin and mucous membranes
Azidothymidine	More common in Fitzpatrick type ≥ III
Bleomycin	With sclerodermatous skin lesions
Busulfan	With skin hyperpigmentation
Cyclophosphamide	With palmo-plantar hyperpigmentation
Daunorubicin	With hand-foot syndrome
Doxorubicin	With hand-foot syndrome
Dacarbazine	With increased photosensitivity
5-Fluoro uracil	Half-and-half nails
Hydroxyurea	Skin hyperpigmentation of skin pits
Psoralens	PUVA freckles
Tegafur	Hyperpigmented macules on the lips, genital, and palmoplantar

The occurrence of streaks on multiple nails is characteristic for hydroxyurea developing in about 4.3% of cases [35, 36] (Fig. 17.6). R-CHOP therapy with cyclophosphamide and doxorubicin has been reported to induce melanonychia of all 20 nails in a patient with non-Hodgkin lymphoma [37].

Xanthochromia (yellow nails) has been observed during long-term treatment with thiol compounds such as D-penicillamine, tiopronin, and bucillamine in rheumatoid arthritis [38]. After withdrawal of bucillamine, in more than 90% of patients, the discoloration disappeared,

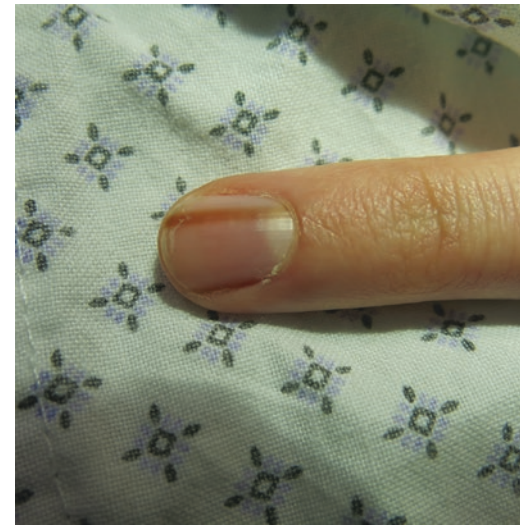

Fig. 17.6 Striated brownish nail plate pigmentation due to hydroxyurea

whereas lymphedema and pulmonary manifestations improved only in 30.8 and 35.0% of the patients, respectively [39]. Yellow nails can be a consequence of systemic treatment with mTOR inhibitors [40].

Reddish or orange pigmentations are due to hemorrhagic suffusions seen with taxanes, bleomycin, cisplatin, and capecitabine [41]. Red nails are sometimes caused by drug-induced subungual pyogenic granuloma. The most important differential diagnosis is the glomus tumor [42].

Leukonychia is the white coloration either by impairment of keratin synthesis (true leukonychia) or by changes in the local blood flow of the nail bed (apparent leukonychia). True leukonychia is not unusual during treatment with antimetabolites (vincristine, cyclophosphamide, etc.). Transverse leukonychia has been observed in patients with polychemotherapy [43] (Fig. 17.7). Antidepressant trazodone is also known to cause true leukonychia [44]. Onycholysis may cause apparent leukonychia when the nail plate becomes separated from the nail bed [45].

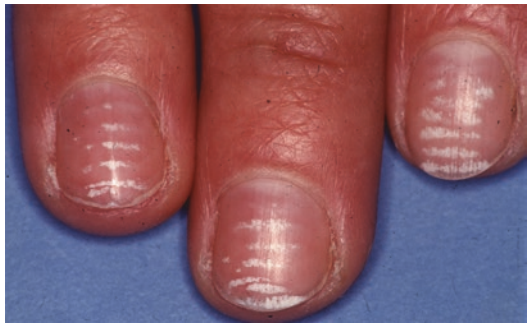

Fig. 17.7 Transverse leukonychia after polychemotherapy

Blue nails can be observed during drug therapy with hydroxyurea, minocycline, and antimalarial drugs [42].

Green nails (chloronychia) can be observed during topical dithranol therapy [3]. Chloronychia occurring during chemotherapy, immunosuppression, or antibiotics is suggestive of *Pseudomonas aeruginosa* infection [46].

Beau's Lines

Beau's lines are transverse linear depression of the dorsal nail plate caused by temporary reduced mitotic activity of the nail matrix. All of the antimitotic drugs can cause Beau's lines. They can affect all nails, but fingernails seem to be more sensitive [45].

In a study from south India, Beau's lines were seen in 11.9% of patients on chemotherapy and in 22% of patients with combined chemo- and radiotherapy [47].

Overcurvature (Pincer Nails)

Reversible transverse overcurvature of the nails (pincer nails) has occasionally been observed after treatment with beta-blockers [48, 49] (Fig. 17.8). The mechanism of this adverse event is unknown. Due to the rarity, risk factors or preventive measures are obscure.

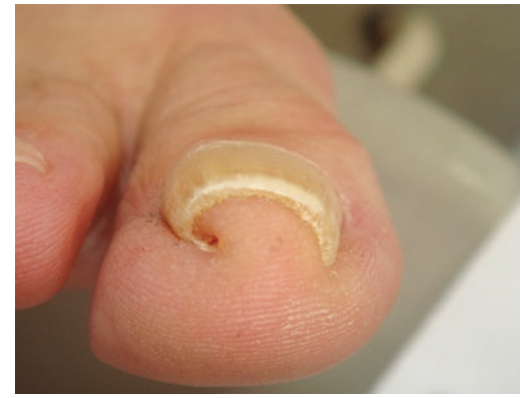

Fig. 17.8 Pincer nail in a patient on metoprolol

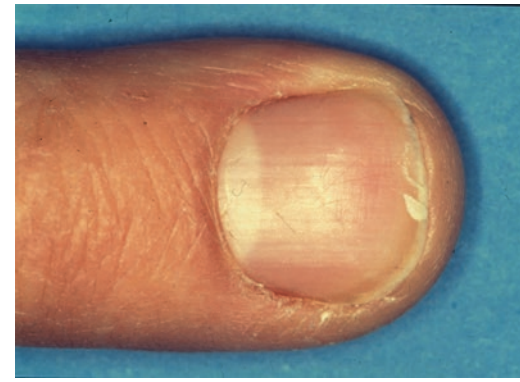

Fig. 17.9 Brittle nail induced by temsirolimus

Brittle Nails and Onychoschizia

In these conditions the distal portion of the nail plate splits horizontally. Brittle nails can be considered the milder type, while onychoschizia is the more severe. Brittle nails are not uncommon during chemotherapy alone or combined with radiotherapy. One study estimated the frequency as high as 8.7% and 15%, respectively [47]. Brittle nails and onychoschizia can be observed in patients treated with mTOR inhibitors such as temsirolimus [40] (Fig. 17.9).

Ibrutinib is a Bruton tyrosine kinase inhibitor approved for certain hematological malignancies. In one study, the drug caused brittle fingernails in

67% of patients at a median of 6.5 months after starting ibrutinib therapy and brittle toenails in 23% after a median of 9 months of ibrutinib therapy [50].

Elkonyxis

Elkonyxis is a nail plate condition with irregular, punched-out defects in the dorsal nail plate. The defect moves distally with the growing nail. This rarely reported feature has been observed with isotretinoin [51, 52].

Median Nail Plate Dystrophy

Median nail plate dystrophy in general is most common on the thumb nails. It has been observed by isotretinoin together with elkonyxis [52]. Alitretinoin and protease inhibitor ritonavir are also capable to induce median nail plate dystrophy [53, 54]. However, this adverse event is rather uncommon (Fig. 17.10).

Fig. 17.10 Median nail plate dystrophy due to isotretinoin

Treatment of Drug-Related Nail Changes

To prevent drug-induced nail changes, patients on photosensitive drug should be instructed to avoid intensive sun exposure or tanning beds. In females, an opaque nail varnish can help to protect the nail bed from sunlight. Photoprotection can prevent drug withdrawal [32].

To avoid paronychia, manicure/pedicure and exposure to wet work should be reduced. The nail folds need a regular skin care with moisturizers. Nail trimming should not traumatize the area [45].

During treatment with taxanes, the percutaneous cooling of fingers and toes seems to be useful to reduce drug-related onycholysis. However, discomfort and frostbites have been observed when wearing frozen gloves and socks [55]. In a trial with 200 patients receiving taxanes, frozen gloves/socks were applied only in hourly taxane-based treatments. However, no statistically significant difference in general nail toxicity incidence and the time to development of nail changes was found between the intervention and the control groups [56]. Further studies are necessary.

For other drugs, cooling the fingers and toes may be a questionable protective approach, since drug concentrations in fingers and toes do not correspond to observed nail toxicities [33].

Another option for patients with targeted therapy-related paronychia or periungual pyogenic granulomas is topical timolol, either alone or in combination with other topical treatments. In an uncontrolled trial, almost two thirds of patients showed at least a partial response after 1 month of therapy with a favorable safety profile [57].

Painful subungual hematoma needs drainage by nail plate punch biopsy [46]. Brittle nails and onychoschizia can be improved by oral biotin [58]. Medical nail lacquers with silica, chitosan, or hyaluronic acid may support improvement of appearance and structure of nail

plates. Camouflage of nail plate color changes by colored nail varnish is an option [45, 59]. Paronychia improves by topical treatment with a combination of corticosteroids and antibiotics [60]. If possible, a dose reduction of the responsible drug should be considered. Pyogenic granuloma has to be treated early by either cold steel or vascular laser [18].

Artificial nails (sculptured nails) cannot recommended as a treatment since these procedures bear a risk of contact sensitization, onycholysis, and infection [61, 62].

Conclusions

Drug-induced changes of nails are common. Drugs associated with nail changes are antibiotics, antidepressants, protease inhibitors, cytotoxic drugs, immune-modulating compounds, or immune checkpoint inhibitors. They often have a negative impact on quality of life. Prevention of such adverse events should be an integral part of drug therapy. Although the management of these cutaneous toxicities has been improved, there is still a lack of knowledge of the underlying mechanism, which would provide the opportunity for a better prevention and care in the future.

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18 Current Applications and Advances in Nail Ultrasound Imaging

Ximena Wortsman

Introduction

The nail is one of the main applications of ultrasound in dermatology due to the possibility to observe in detail both the nail plate and the nail bed with high definition [1, 2]. These capabilities allow reducing potential cosmetic sequels secondary to biopsies, besides becoming a powerful diagnostic and monitoring tool for common ungual conditions [1, 3].

To date, ultrasonography can support the diagnosis in a wide range of ungual pathologies such as benign and malignant tumors, inflammatory diseases, and location abnormalities [1, 4–6]. Ultrasound can also discriminate between degenerative and inflammatory conditions [7].

During the last decade, ultrasound has significantly improved in the resolution and detection of vascularity. Thus, devices working with high-frequency probes that can vary between 15 and 70 MHz allow discriminating structures that measure 30 μm [8]. Moreover, the new types of vascularity software can detect the slow flow running in submillimeter vessels [8].

The ultrasonographic assessment of the lesional origin (ungual or periungual), size in all axes (mm), exact location (proximal, distal, central or eccentric, radial or ulnar, medial or lateral), degree of vascularity, and involvement of adjacent tissues can help to select the site and the extent of the incision and have a well-informed presurgical plan [5, 9]. Moreover, for example, in glomus tumors, it has been reported that the patients with presurgical ultrasound examination present a lower rate of recurrence in comparison with cases that did not have previous imaging examinations [10].

The imaging patterns of lesions in several ungual diseases have been described in a growing list of publications [1, 6, 9, 11–16], which now includes ultrasonographic diagnostic criteria for several of them [17].

Besides the detection of abnormalities in the nail and periungual tissues, ultrasound provides useful data about alterations in the digital skin, joints, tendons, and bony margin [6]. This capability is helpful for the detection of psoriatic arthropathy, which can be relevant in cases that may benefit from more aggressive medications [13].

This chapter aims to review the ultrasonographic advances for nail conditions.

Technical Considerations

This type of examination requires specialized equipment that includes multichannel devices working with linear or compact linear probes that can range in their highest frequency between 15

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and 70 MHz [1, 17, 18]. These high-frequency probes present higher resolution, but their penetration into the tissues is lower; however, most of the machines come with two or three probes that allow moving through a wide range of depth, maintaining a high-definition image through all the layers.

Ideally, the operator of the machine should be trained in imaging and dermatology because there is a gathering of clinical and ultrasonographic information. The possibilities for training in dermatologic ultrasound have substantially increased during the last decade, and besides the significant increment of publications on this topic, there are several annual sessions and courses, some of them under the umbrella of well-known international scientific societies such as the American Institute of Ultrasound in Medicine (AIUM; www.aium.org) or the European Federation of Societies for Ultrasound in Medicine and Biology (EFSUMB; www.efsumb.org) [19].

Examination Technique

The hands and feet need to be in an extended position. For examining the thumbs, it is necessary to use a towel or pad to stabilize the fingers. A copious amount of gel is applied on top of the nail and periungual regions for allowing the passing of the sound waves into the tissues. Then, the operator performs a broad sweep with the probe that includes at least two perpendicular axes. This protocol follows a standardized sequence that starts with grayscale and is followed by a color Doppler and spectral curve analysis. Thus, it is possible to know in advance the presence of hypervascular or hypovascular areas, the type (arterial or venous), and velocity of the flow (cm/sec). Panoramic views, 3D reconstructions, and microvasculature analyses can provide better information or understanding of the characteristics and extent of lesional tissue [1, 17, 18].

Ultrasound Normal Anatomy of the Nail

At 15–18 MHz, the nail plate is observed as a hyperechoic bilaminar structure that presents an outer plate, also called a dorsal plate, and an inner plate, named ventral plate. An anechoic interplate space is located in between the dorsal and ventral plates. However, at 70 MHz, the anechoic interplate space becomes more hyperechoic but less intense than the outer and inner borders of the nail plate [17]. This ultrasonographic appearance has been related to the presence of hard and soft keratin within the nail plate.

The nail bed shows as a hypoechoic space beneath the nail plate that turns to slightly hyperechoic in the proximal part where the matrix region is located [1, 17].

The periungual tissues present the same echostructure of the normal skin, which is a laminar hyperechoic epidermis, and a hyperechoic dermal band, less bright than the epidermis [1, 17, 18].

Arterial flow comes from the digital arteries that supply the nail through the proximal part. Venous flow drains through the digital veins [1, 17, 18].

The bony margin of the distal phalanx presents as a hyperechoic line underneath the distal phalanx [1, 2, 17, 18].

The extensor tendons present a homogeneous fibrillar hyperechoic pattern that shows anisotropy artifact in the distal insertion due to the oblique disposition of the tendons in this part [1, 2, 16].

The joint spaces are slightly perceptible, and occasionally, submillimetric anechoic laminar fluid may be detected [1, 2, 16].

The bony margin of the distal phalanx presents as a hyperechoic line underneath the distal phalanx (Figs. 18.1, 18.2, and 18.3) [1, 3, 17, 18, 20].

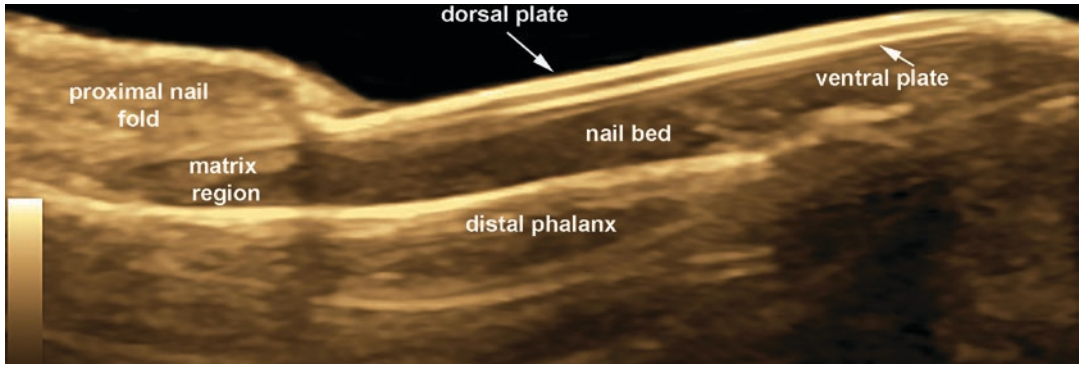

Fig. 18.1 Normal ultrasonographic anatomy of the nail using an18 MHz maximum frequency probe (longitudinal view)

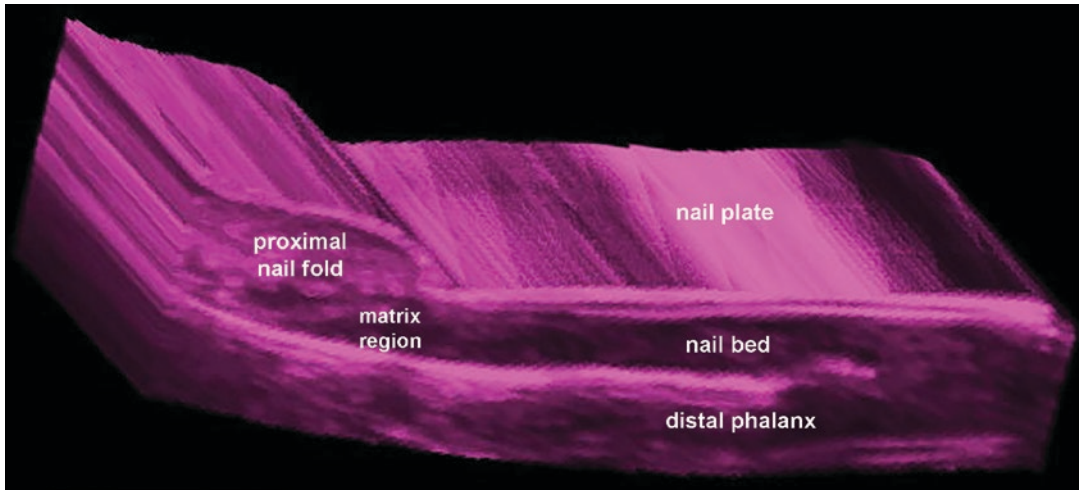

Fig. 18.2 3D normal ultrasound anatomy of the nail (18 MHz)

Main Applications and Advances of Ultrasound of the Nails

Growth and Location Alterations

Onychocryptosis

Ultrasonography can detect the location and size of the fragment of the nail plate embedded in the lateral periungual region. Since many of these cases are seen in the emergency departments, the ultrasound examination could facilitate the diagnosis and removal of the fragment.

The fragments appear as bilaminar hyperechoic structures within the lateral nail fold. Commonly, there is a hypoechoic thickening or band as well as mild hypervascularity of the periungual dermis due to inflammation (Fig. 18.4) [17, 18, 21].

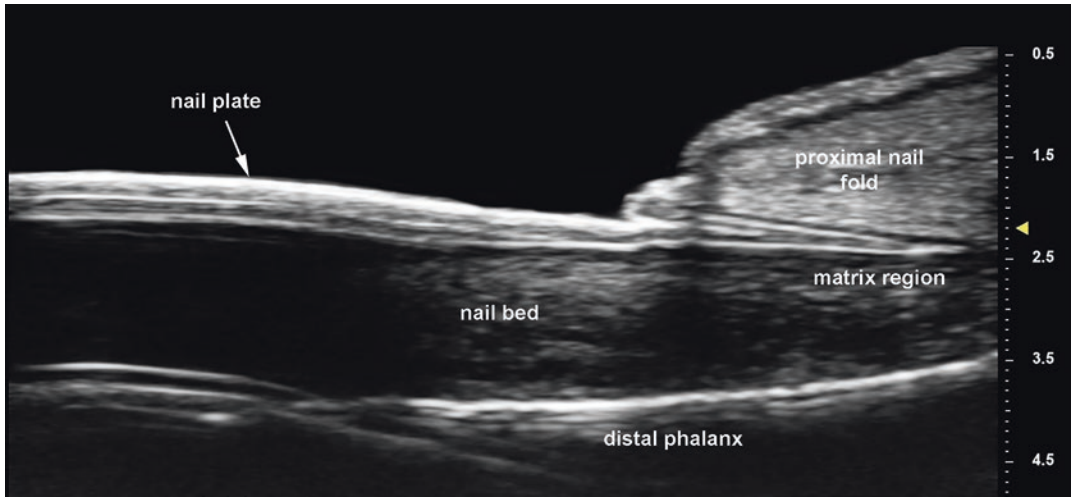

Fig. 18.3 Normal ultrasound anatomy of the nail using a 70 MHz maximum frequency probe (longitudinal view)

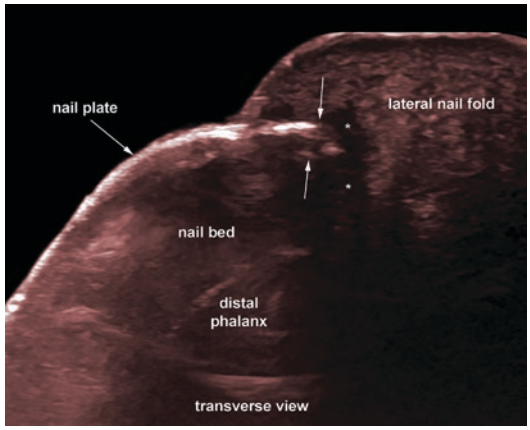

Fig. 18.4 Onychocryptosis. Ultrasound image (18 MHz; transverse view; colored; right big toe) shows hyperechoic and irregular fragment (vertical arrows pointing up and down) embedded in the lateral nail fold. Notice the hypoechoic band (*) in the dermis of the lateral nail fold that corresponds to inflammation

Onychomadesis

The fragmentation of the nail plate is commonly associated with inflammation of the nail bed. On ultrasonography, there are thickening and hypoechogenicity of the nail bed that involves the matrix region. The nail plate is thick and fragmented, and the fragmentation usually starts in the ventral plate (Fig. 18.5) [17, 18, 21].

Retronychia

The posterior embedding of the nail plate can be detected alone or concomitant with onychomadesis. In literature, there are three diagnostic ultrasound criteria for unilateral retronychia: the decrease of the distance between the origin of the plate and the base of the distal phalanx in comparison with the healthy site, the presence of a hypoechoic halo surrounding the origin of the nail plate, and the thickening of the proximal nail fold in the affected side [4, 17]. The ultrasound diagnosis of retronychia needs at least two of these signs, being the halo sign a constant finding [14]. These criteria may help when there is an upward displacement of the nail plate secondary to prominent inflammation. In bilateral retronychia, there are published ultrasound criteria that may help and include, besides the halo sign (constant), a distance between the origin of the nail plate and the base of the distal phalanx $\leq$5.1 mm in big toes and thumbs and/or a difference of $\geq$0.5 mm of this distance between the affected nail (with decreased distance) and the contralateral healthy nail.

Other criteria are a proximal nail fold thickness of $\geq$2.2 mm for male or $\geq$1.9 mm for female patients and/or a proximal nail fold $\geq$0.3 mm thicker in comparison with the contralateral healthy nail (Figs. 18.6, 18.7, and 18.8) [4, 14, 17, 22–24].

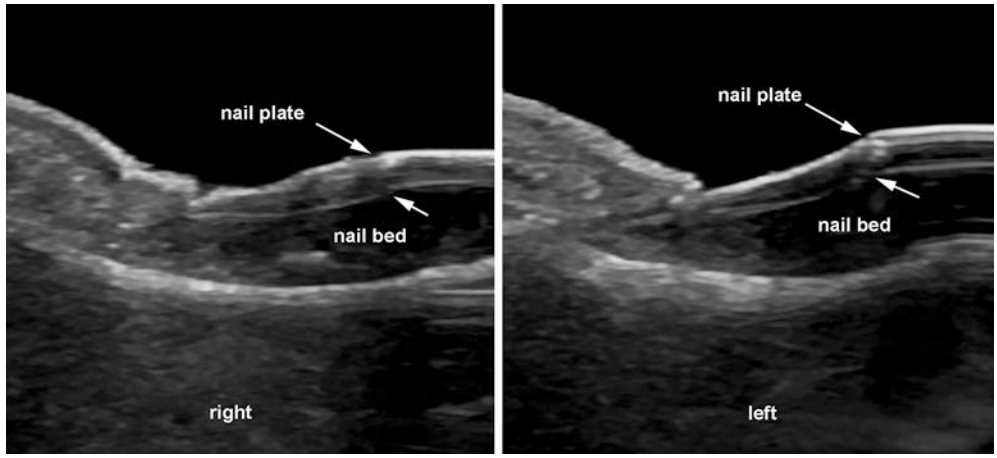

Fig. 18.5 Onychomadesis. Grayscale ultrasound (comparative side-by-side; longitudinal views; big toes) shows fragmentation of the nail bed at both sides, slightly more prominent on the left. The nail bed is thick and hypoechoic, and the nail plates also show increased thickness and irregularities

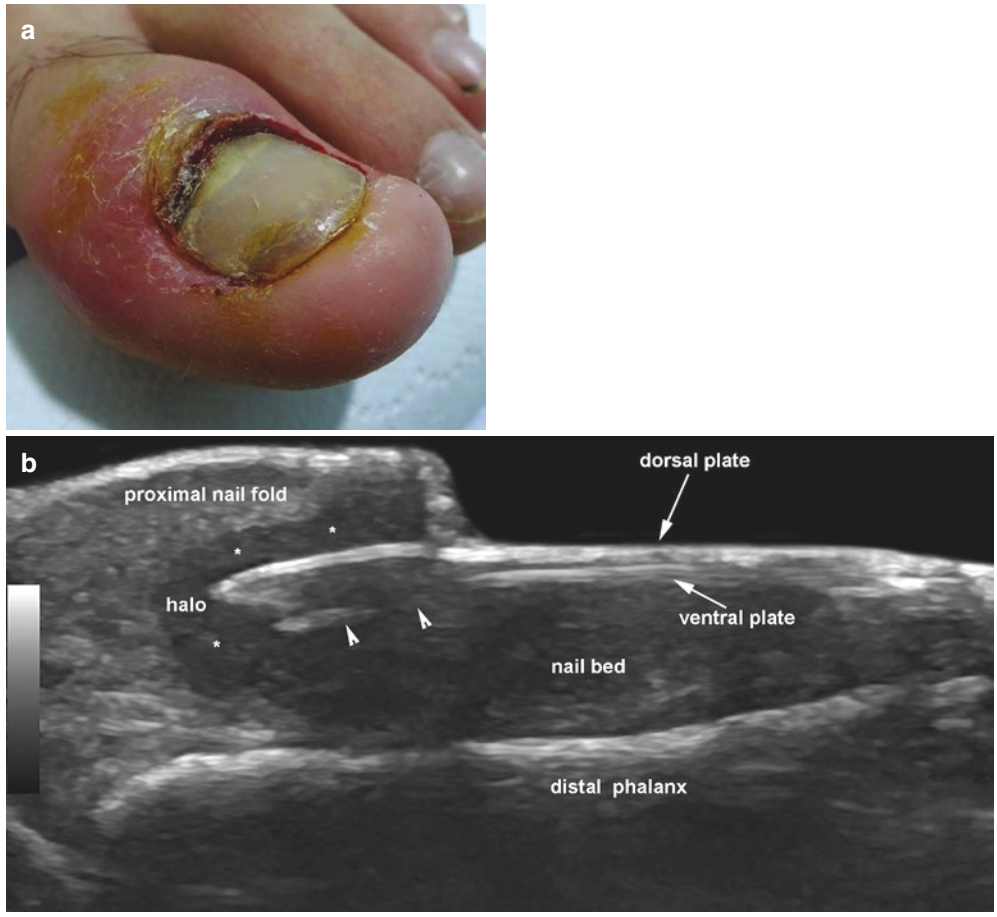

Fig. 18.6 (**a**, **b**) Retronychia. (**a**) Clinical photograph and (**b**) grayscale ultrasound image (longitudinal view; left big toe; 18 MHz) present embedding of the nail plate into the proximal nail fold. There is a fragmentation of the ventral plate (arrowheads) and a hypoechoic band (*) surrounding the origin of the nail plate. Increased thickness and decreased echogenicity of the dermis at the proximal nail fold seen

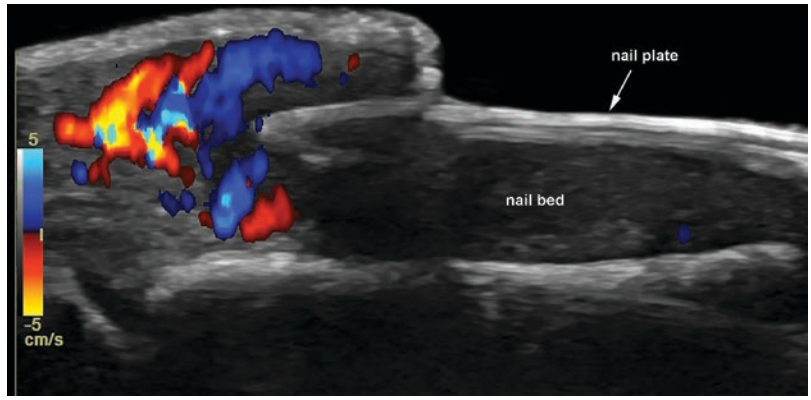

Fig. 18.7 Retronychia. Color Doppler ultrasound of the same case of Fig. 18.6 shows increased vascularity at the proximal nail fold that surrounds the origin of the nail plate

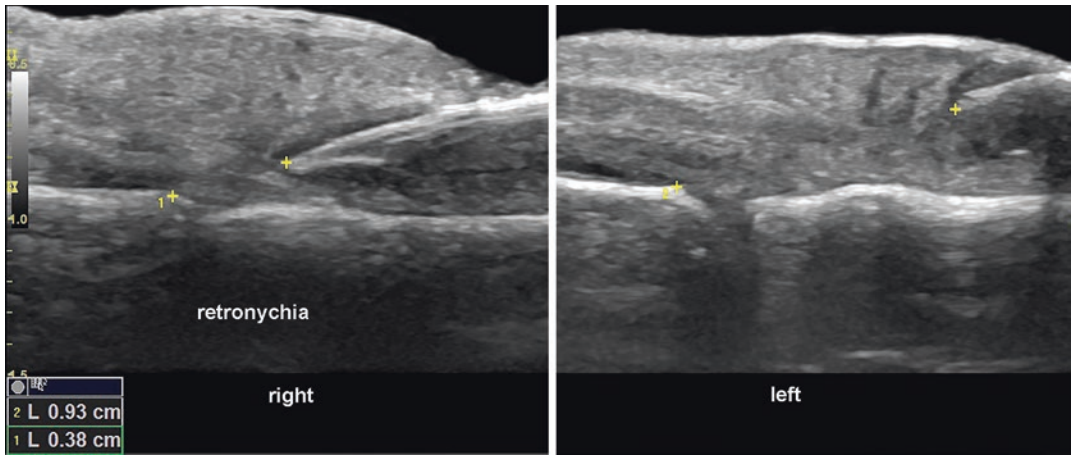

Fig. 18.8 Retronychia. Ultrasound grayscale comparative side-by-side measurement of the distance between the origin of the nail plate and the base of the distal phalanx. Notice the decreased length of the right side that corresponds to the retronychia (0.38 cm versus 0.93 cm)

Inflammatory Conditions of the Nail

Psoriasis

Ultrasonography can help to diagnose psoriatic onychopathy, and the following signs have been reported: thickening of the nail bed, loss of definition of the ventral plate, hyperechoic deposits in the distal part of the ventral plate, and the presence of thick, irregular, and wavy nail plates [1, 6, 17, 18, 25]. On color Doppler, there is hypovascularity or hypervascularity of the nail bed according to the degree of inflammation (Figs. 18.9 and 18.10) [6, 25]. Moreover, ultrasound can also show the affection of other structures such as the skin, joints, tendons, and bony margin (Fig. 18.11) [6]. Thus, the assessment of synovitis, tendinopathy, and erosions can support the diagnosis of psoriatic arthropathy, which could imply the management of the patient with more aggressive medications [6, 15, 26–32]. On the other hand, the presence of psoriatic onychopathy seems to be a good predictor of severity and psoriatic arthropathy [33]. The examination is usually performed in all the nails; therefore, the involvement of ≥3 nails can be detected earlier, which may help to discriminate better the patients with more severe forms of presentations [34]. Regarding the ultrasonographic differential diagnosis between psoriasis and onychomycosis, there is

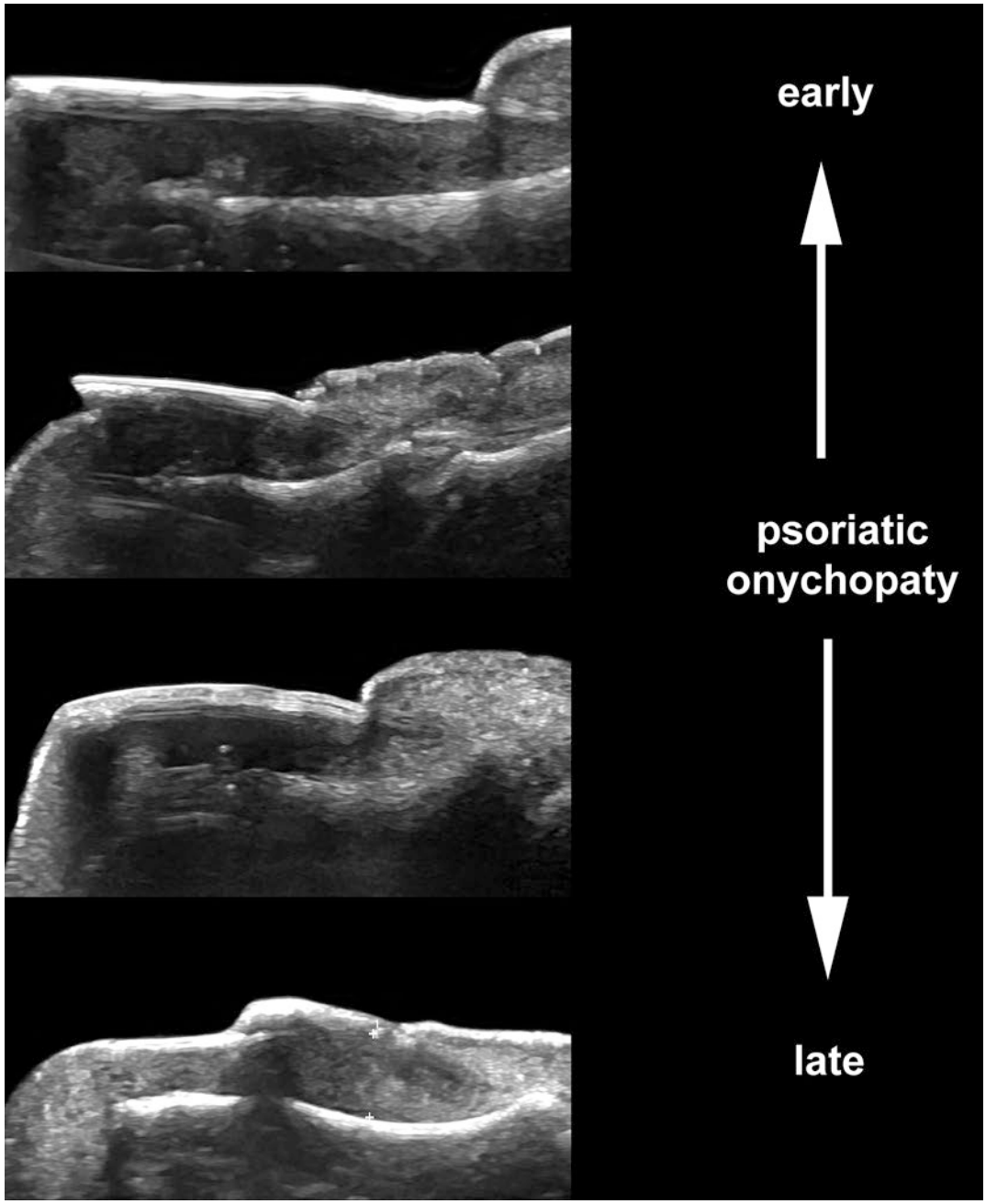

Fig. 18.9 Psoriasis. Ultrasound grading of severity in psoriatic onychopathy

little information in the literature [29] and commonly, these two entities are associated [35]; therefore, the discrimination could be complicated. Furthermore, the patients go to the ultrasound examination after the fungus test is negative and/or they have received antimycotic treatment for several months. In our experience, onychomycosis tends to affect the superficial nail bed and the nail plate, in contrast to psoriasis that affects the whole thickness of the nail

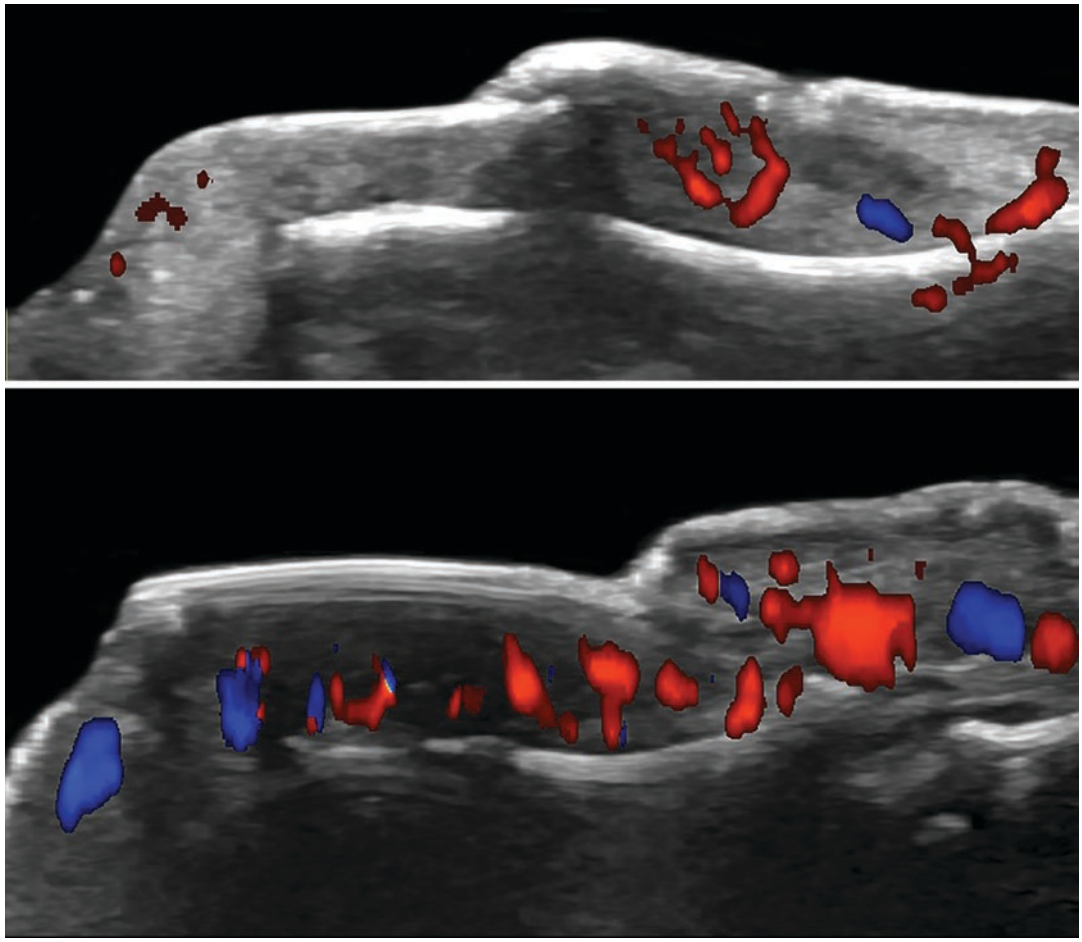

Fig. 18.10 Psoriasis. Color Doppler ultrasound grading of vascularity in psoriatic onychopathy

bed, besides the nail plate [6, 13, 15, 17, 18, 25, 26, 28–30]. Ultrasound has been additionally used for monitoring biologic drugs in psoriatic onychopathy [36].

Morphea/Scleroderma

Increased thickness and hypoechogenicity of the nail bed with an upward displacement of the nail plate are common findings in morphea or scleroderma [17, 37]. On color Doppler, hypovascularity of the nail bed is frequent, particularly in patients with Raynaud syndrome. Decreased echogenicity of the periungual dermis and increased echogenicity of the subcutis of the fingers with loss of the dermal-hypodermal borders are also detected (Fig. 18.12) [17, 18].

Fluid Collections

Anechoic laminar subungual collections are possible to detect in the nail bed. In cases with purulent material, the content may be hypoechoic. On color Doppler, there is hypovascularity or hypervascularity of the nail bed according to the degree of inflammation (Fig. 18.13) [17, 18, 21].

Median Canaliform Dystrophy

The thinning of the proximal and central part of the nail bed that includes the matrix region is a common finding in this condition. Central irregularities and loss of the bilaminar structure of the nail are additional findings. On color Doppler, these cases tend to present a hypovascular nail bed to scarring (Fig. 18.14) [17, 18].

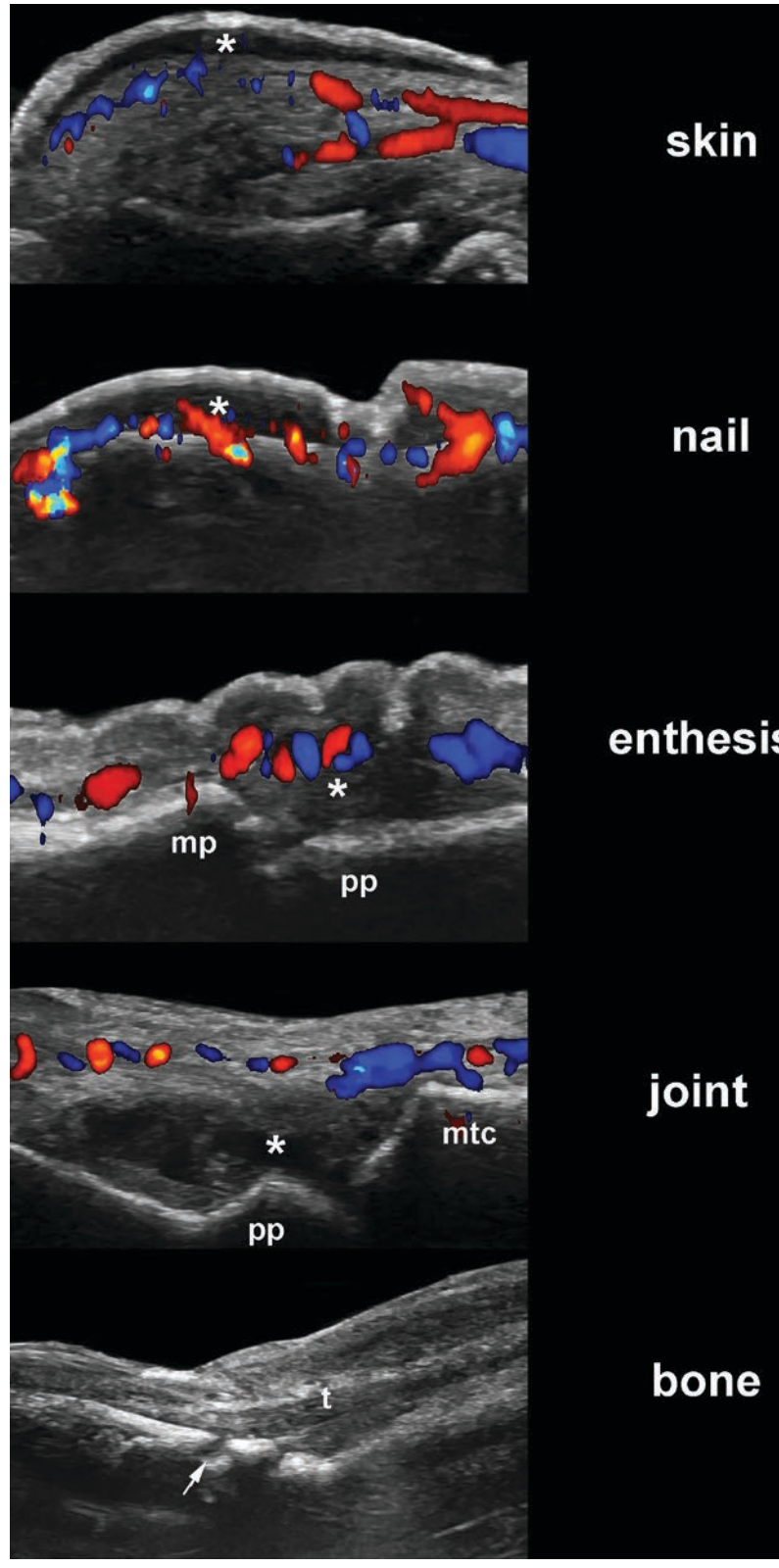

Fig. 18.11 Ultrasonographic alterations of tissues in psoriasis. Active psoriatic changes (color Doppler and grayscale) in the skin (cutaneous plaque), nail (onychopathy), enthesis (tendinopathy), joint (synovitis), and bone (erosion marked with an arrow)

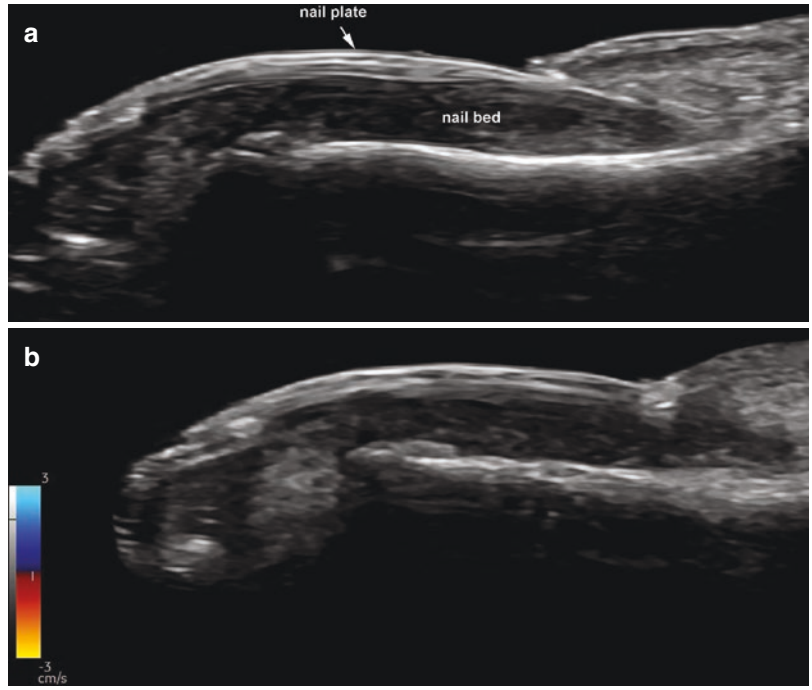

Fig. 18.12 (**a**, **b**) Morphea. (**a**) Grayscale and (**b**) color Doppler ultrasound demonstrate slightly increased thickness and hypovascularity of the nail bed (**b**)

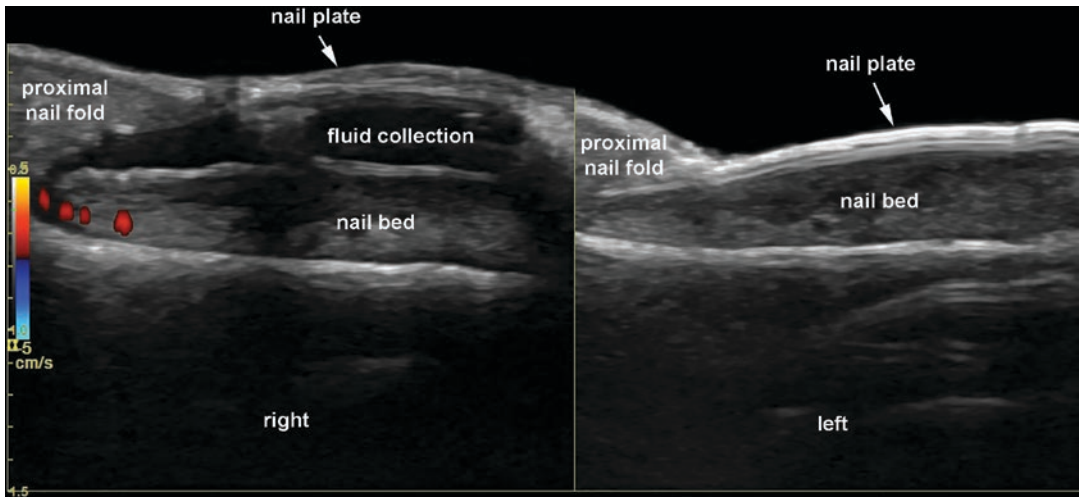

Fig. 18.13 Subungual fluid collection. Color Doppler ultrasound comparative side-by-side longitudinal view shows an anechoic band that corresponds to a fluid collection in between the nail plate and the nail bed at the right side

Subungual Warts

These are secondary to human papillomavirus infections and commonly affect the periungual and ungual regions [38, 39]. On ultrasound, they presentsimilar morphology to warts on other locations of the body, which includes a fusiform shape and hypoechoic subungual and/or periungual structure with irregularities of the nail plate (Fig. 18.15 and 18.16) [17, 18].

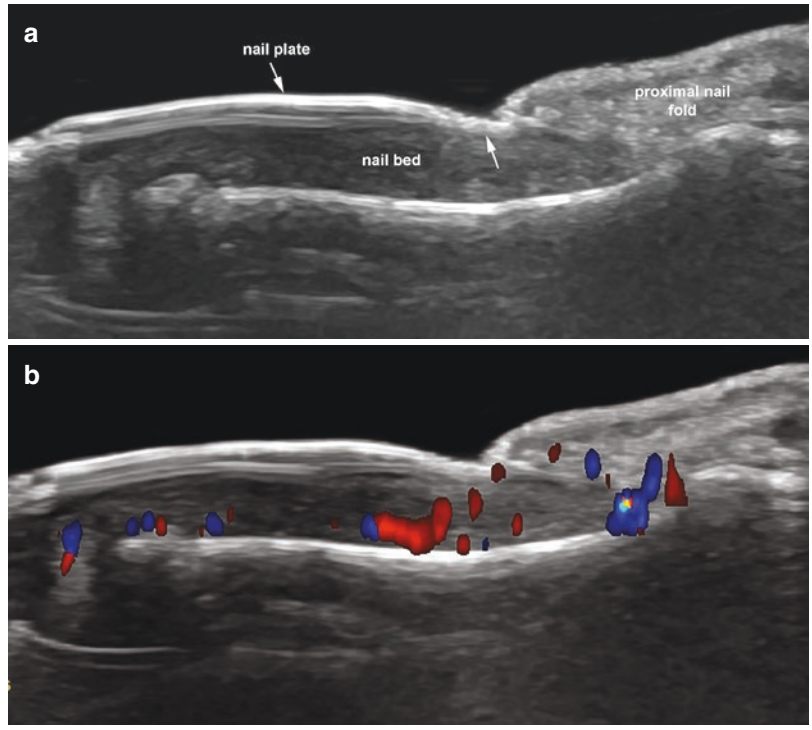

Fig. 18.14 (**a**, **b**) Median canalicular dystrophy. (**a**) Grayscale ultrasound demonstrates heterogeneous echogenicity and thickening of the proximal part of the nail bed with irregularities of the proximal part of the nail plate (central part). (**b**) Color Doppler ultrasound presents hypervascularity of the proximal nail bed and the dermis of the proximal nail fold

Benign Tumors and Pseudotumors

We will review the most common requests for an ultrasound examination. For academic purposes, the conditions are divided according to their main origin into ungual and periungual [5, 17, 18].

Ungual Origin

These are separated according to nature in solid and cystic.

Solid

Glomus Tumors

These are tumors derived from the neuromyoarterial plexus, and their most common location is the nail. Almost 70% of cases are located at the proximal part of the nail bed (central or eccentric), and the remaining percentage is reported to show a distal location. On ultrasound, the most common form of presentation is a well-defined oval-shaped nodule in the nail bed that generates scalloping of the bony margin of the distal phalanx [5, 10, 11]. *Occasionally, cases with multiple glomus tumors have been described in the literature* [40]. *On color Doppler, they tend to be hypervascular with slow-flow arterial vessels; however, some rare variants such as glomangiomyomas may show hypovascularity* (Fig. 18.17) [5, 10, 11, 17, 18].

Fibromatous Tumors

These comprise a heterogeneous group of benign entities that can present as subungual or periungual eccentric hypoechoic structures or bands. Subungual fibromas tend to affect the lateral nail fold and present as ill-defined or lobulated areas that compress the nail plate and remodel the bony margin. Periungual fibromas commonly present as well-defined band-like structures and involve the proximal nail fold where they contact and extrinsically compress the origin of the nail plate. Fibrokeratomas can show an irregular hyperechoic area in their distal part due to the presence of hyperkeratosis. On color Doppler, fibromas are commonly hypovascular. However, some variants, such as angiofibromas, can be associated with prominent vessels (Figs. 18.18 and 18.19) [5, 17, 18].

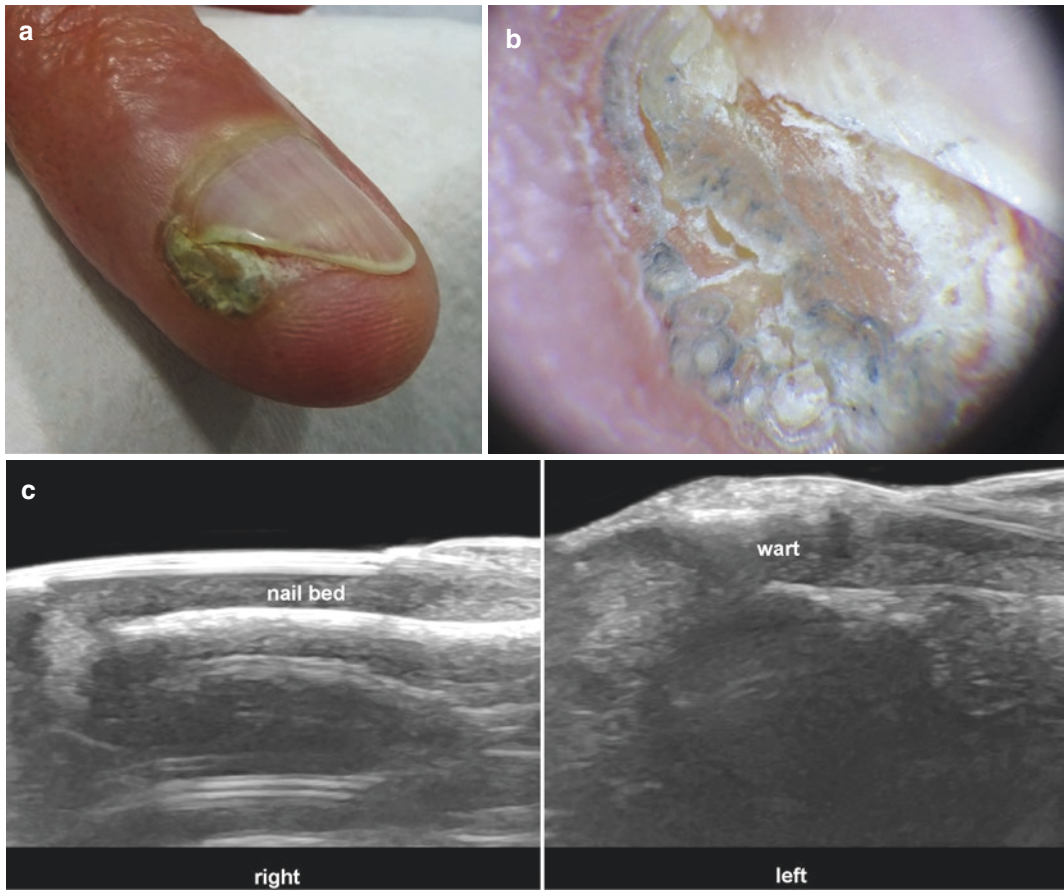

Fig. 18.15 (**a**–**c**) Subungual wart. (**a**) Clinical, (**b**) dermoscopy, and (**c**) ultrasound (grayscale, side-by-side comparative images; right versus left ring fingers) present at the left side a hypoechoic and fusiform thickening of the nail bed with irregular thickening of the nail plate (wart region)

Onychomatricoma

This tumor is derived from the nail matrix, and its ultrasound morphology is characterized as an ill-defined, eccentric, and proximal hypoechoic structure with hyperechoic lines that protrude into the nail plate. On color Doppler, its vascularity can be variable, which can go from hypovascular to an intermediate degree of vascularity (Fig. 18.20) [5, 17, 18, 41].

Granuloma

This pseudotumor is usually associated with chronic inflammation and appears on ultrasound as an ill-defined thickening and hypoechogenicity of the nail bed that displace the nail plate upward. On color Doppler, their vascularity is variable and can go from hypovascular to hypervascular (telangiectatic or pyogenic variant).

Some telangiectatic subungual granulomas may mimic amelanotic melanoma due to their intense hypervascularity. These telangiectatic

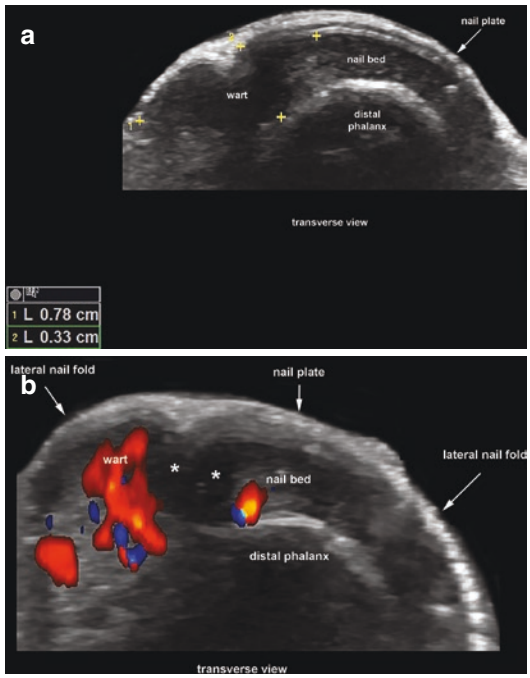

Fig. 18.16 (**a**, **b**) Subungual and periungual wart. (**a**) Grayscale and (**b**) color Doppler ultrasound (transverse view; left ring finger) of the same case of Fig. 18.15 demonstrate hypoechoic fusiform thickening of the nail bed and periungual dermis of the lateral nail fold (radial border). Notice the subungual and dermal hypervascularity in **b**

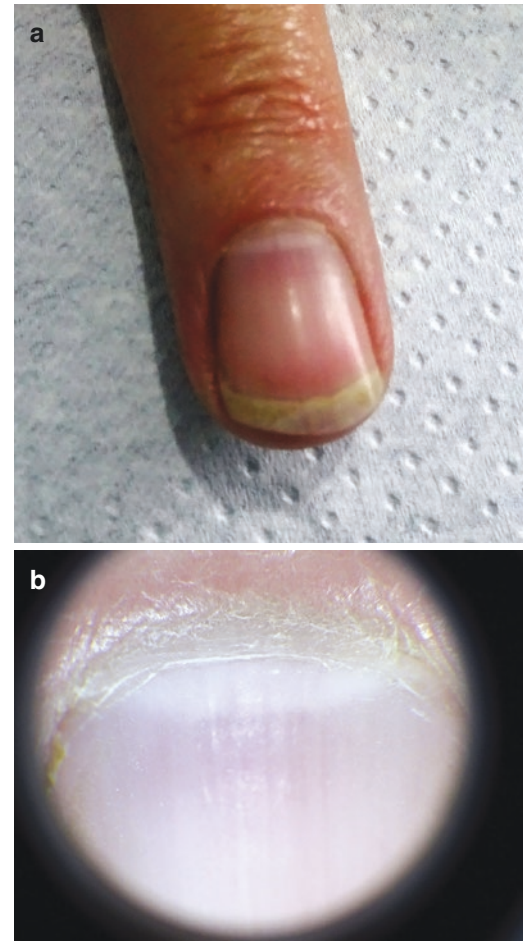

Fig. 18.17 (**a**–**f**) Glomus tumor (left ring finger). (**a**) Clinical photograph. (**b**) Dermoscopy image. (**c**, **d**, and **f**) Ultrasonographic longitudinal views (**c**, grayscale ultrasound at 18 MHz; **d**, color Doppler ultrasound at 18 MHz; **e**, grayscale side-by-side comparative images; and **f**, color Doppler ultrasound at 70 MHz). Notice the well-defined, oval-shaped hypoechoic structure (*, between markers) located in the proximal part of the nail bed. There is hypervascularity within the nodule in **d** and **f**

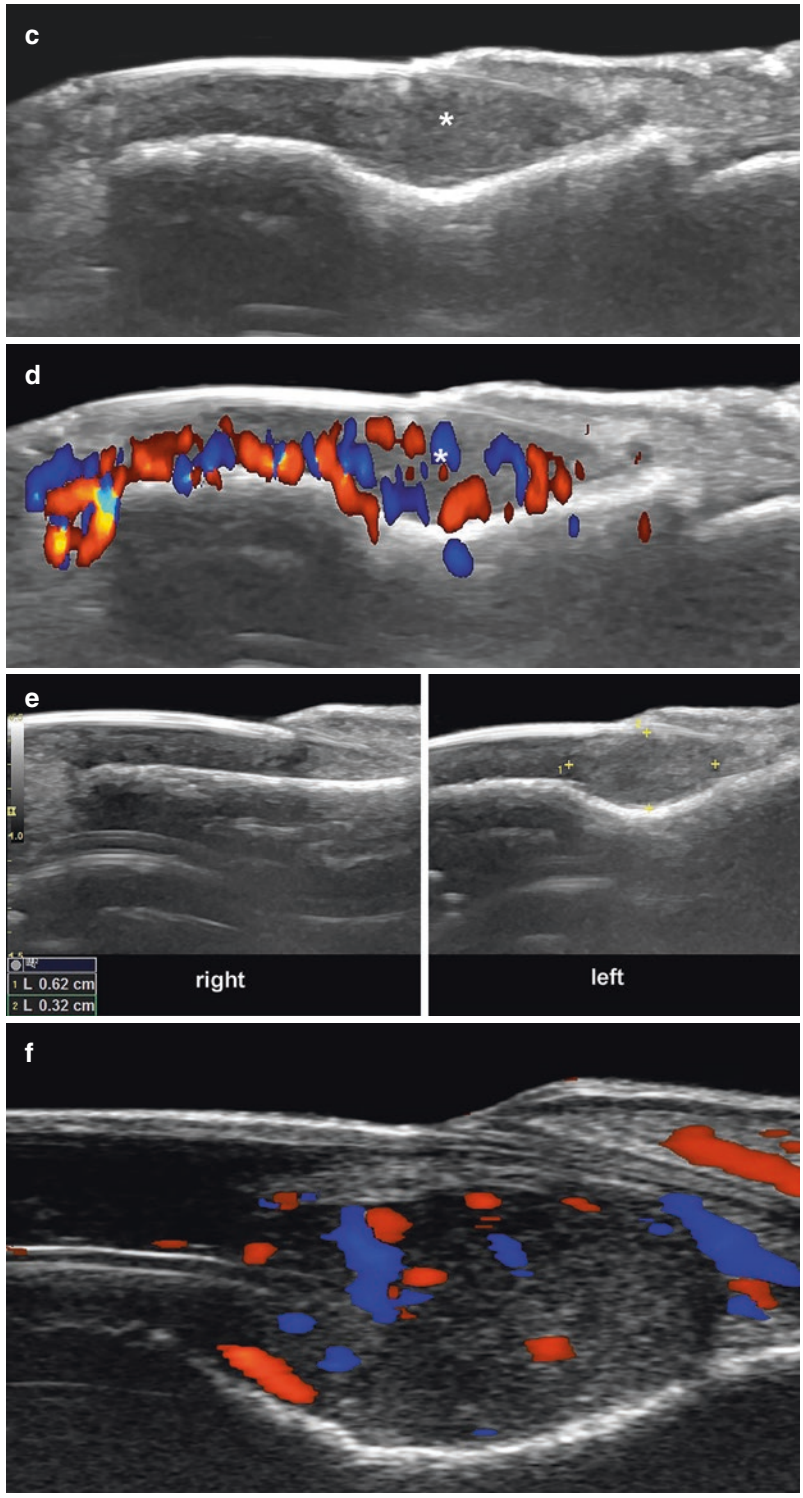

Fig. 18.17 (continued)

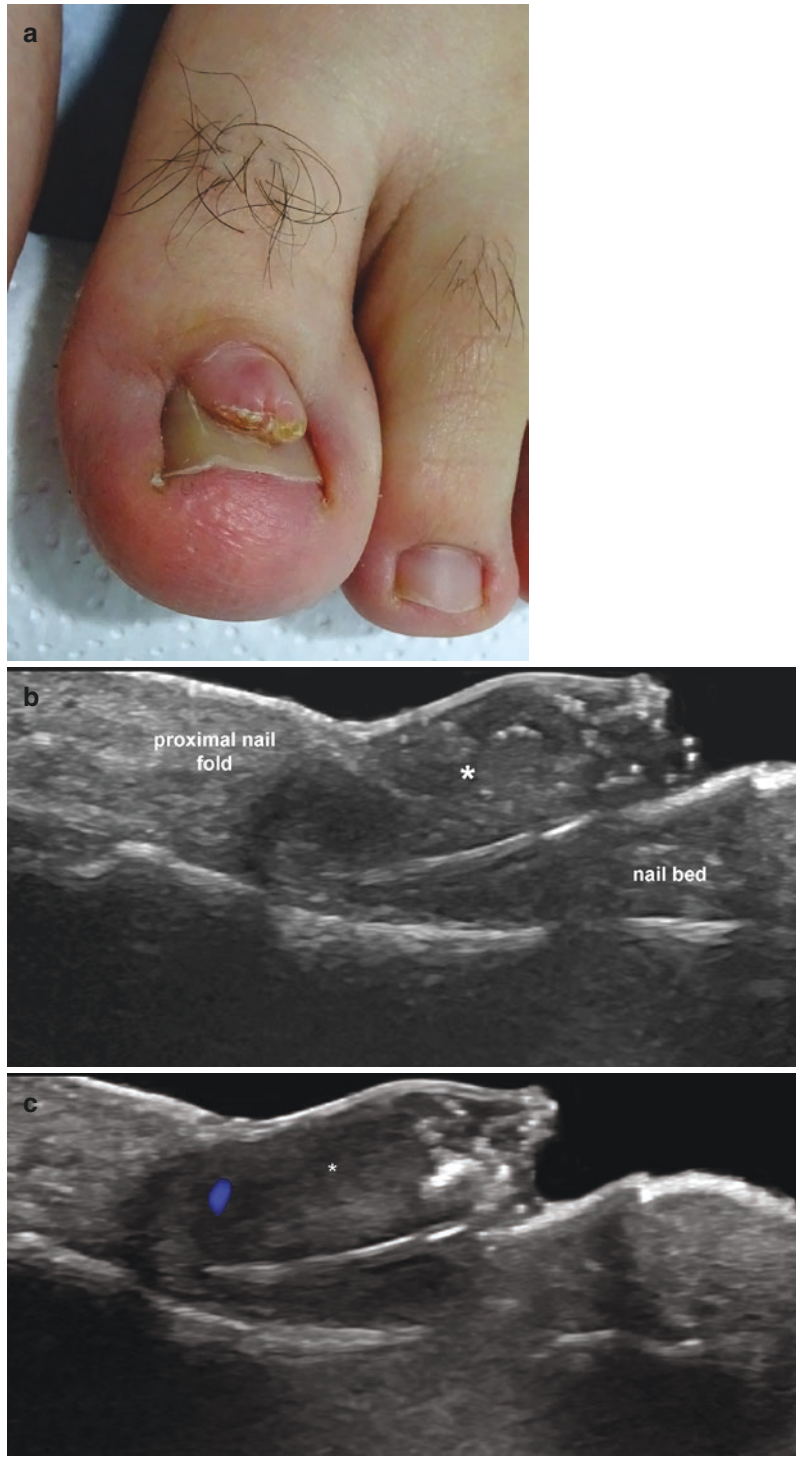

Fig. 18.18 (**a**–**e**) Periungual fibroma (left big toe). (**a**) Clinical photograph. (**b**–**e**) Ultrasound images (**b**–**d**, longitudinal views; **e**, transverse view; **b**, **d,** and **e**, grayscale; and **c**, color Doppler) present band-like hypoechoic structure (*) at the proximal nail fold compressing the proximal part of the nail plate and attached to the proximal part of the nail bed. Notice the hypovascularity of the tumor in **c**

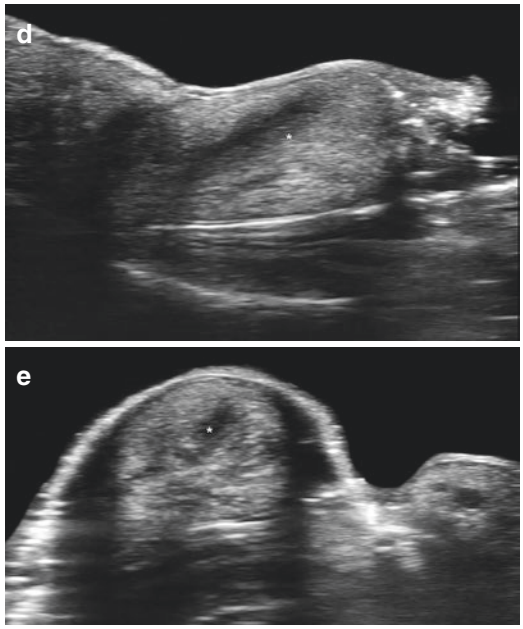

Fig. 18.18 (continued)

granulomas can also affect the proximal nail fold (Fig. 18.21) [5, 17, 18].

Cystic

Mucous Cysts

These are originated by degeneration of the collagen of the nail bed. On ultrasound, they show as oval- or round-shaped anechoic subungual structures that displace the nail plate upward and may present internal echoes. Mucous cysts commonly affect the nail matrix region and generate irregularities of the nail plate and do not connect with the interphalangeal joint. On color Doppler these cysts are avascular (Fig. 18.22) [17, 18].

Periungual Origin

Subungual Exostoses

These benign bony outgrowths derived from the distal phalanx and protrude into the nail bed. On ultrasound, they appear as hyperechoic irregular

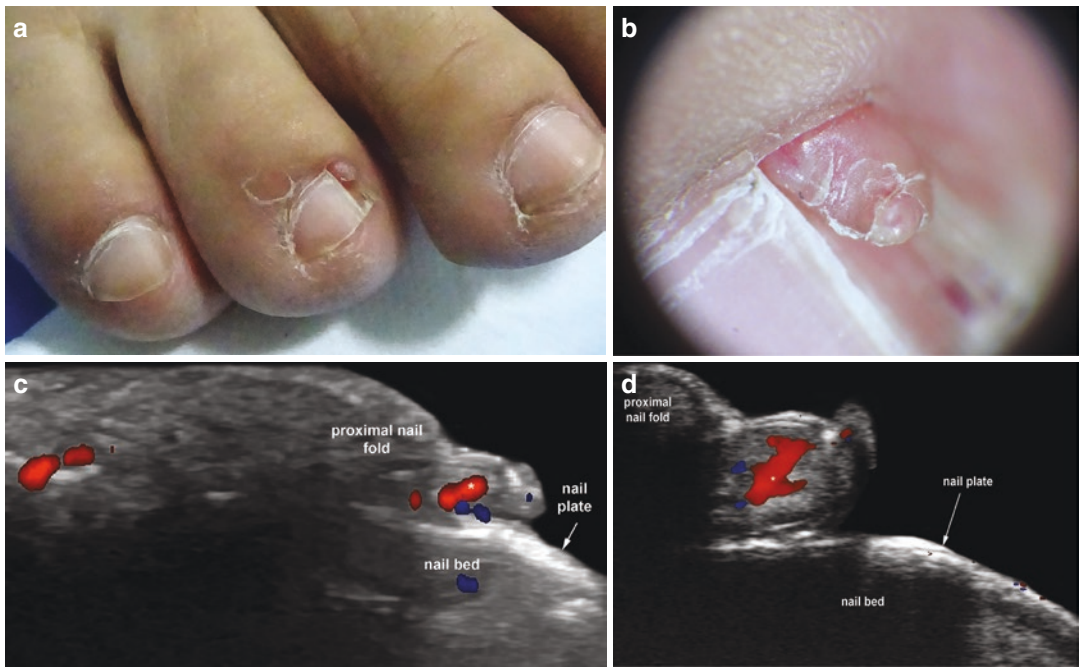

Fig. 18.19 (**a**–**d**) Periungual angiofibroma (right fourth toe). (**a**) Clinical photograph. (**b**) Dermoscopy. (**c** and **d**) Color Doppler ultrasound images (**c**, at 18 MHz; **d**, at 70 MHz) show hypoechoic band-like structure (*) with central vascular pedicle (in colors)

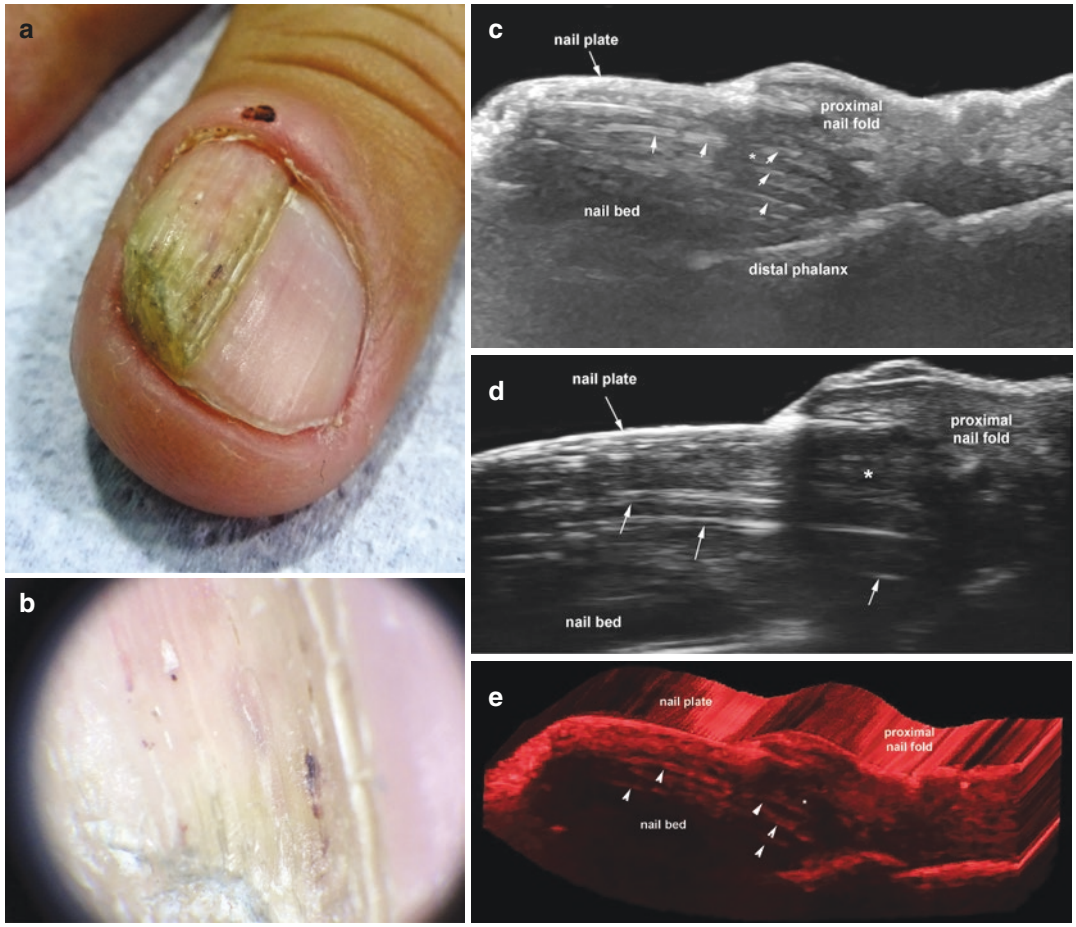

Fig. 18.20 (**a**–**e**) Onychomatricoma (left middle finger). (**a**) Clinical photograph. (**b**) Dermoscopy. (**c**, **d** and **e**) Ultrasound images (longitudinal views; **c**, 18 MHz, **d**, 70 MHz, and **e**, 3D reconstruction at 18 MHz) show hypoechoic subungual structure (*) in the radial aspect with hyperechoic lines (arrows and arrowheads) that protrude into the nail plate

bands that generate posterior acoustic shadowing due to the calcium of the bone. Osteochondromas may also present as a hyperechoic band with posterior acoustic shadowing, and the cartilaginous part of the tumor usually shows a hypoechoic cap. The nail bed is commonly thick and hypoechoic because it presents a secondary inflammatory and granulomatous reaction. According to the degree of affection of the nail matrix, there is a variable amount of thickening and irregularities in the nail plate (Fig. 18.23) [17, 18].

Synovial or Myxoid Cysts

These pseudotumors are originated in the distal interphalangeal joint, and its synovium and fluid extend into the proximal nail bed. Occasionally

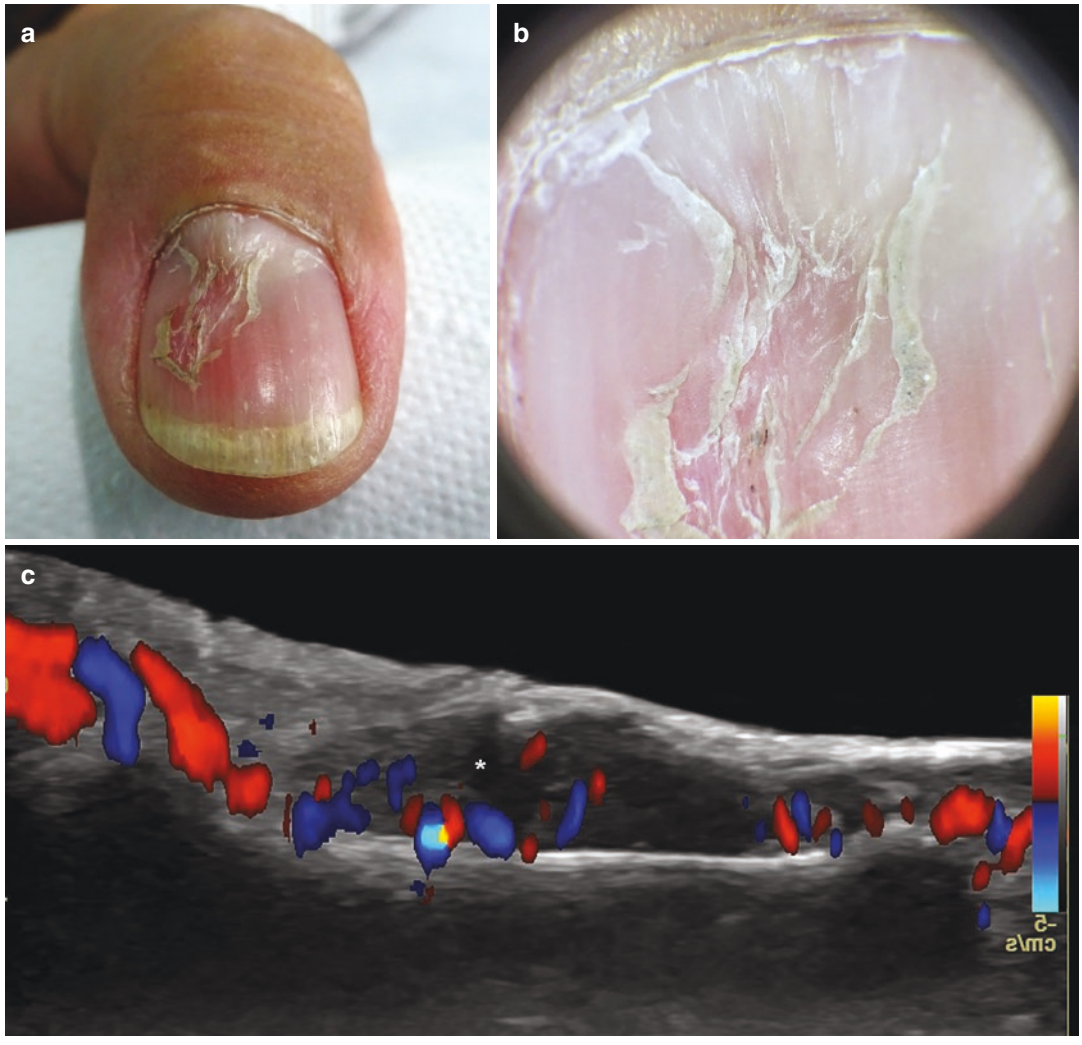

Fig. 18.21 (**a**–**c**) Subungual granuloma (left thumb). (**a**) Clinical photograph. (**b**) Dermoscopy. (**c**) Color Doppler ultrasound (longitudinal view) demonstrates hypoechoic thickening (*) and mild hypervascularity of the proximal part of the nail bed that involves the matrix region and displaces the nail plate upward. Notice the increased thickness and irregularities of the nail plate

these cystic lesions can protrude into the nail bed. On ultrasound, they show as a well-defined oval-shaped structure with internal echoes and connected with the joint through a thin duct. Sometimes there are two or more connections to the joint, and commonly, there are degenerative signs in the distal interphalangeal joint (DIP) with anechoic fluid, prominent hypoechoic synovium, and hyperechoic periarticular osteophytes. Ultrasound can support the diagnosis and locate the site of the connection to the DIP. Due to the extrinsic compression of the nail plate, there is a distal concavity of the bilaminar ungual structure that follows the axis of the cyst. On color Doppler, these cysts are avascular; however, hypervascularity of the proximal nail fold can be detected according to the level of inflammation (Fig. 18.24) [17, 18].

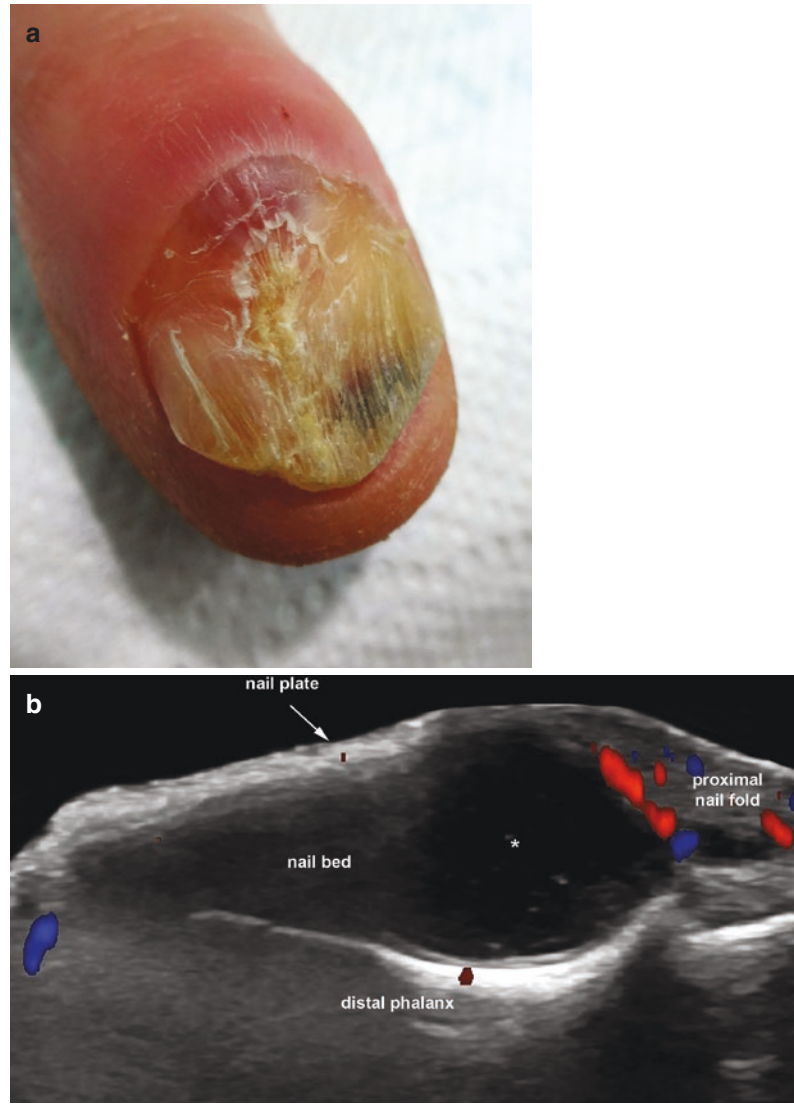

Fig. 18.22 Mucous cyst (**a**, **b**) (right index). (**a**) Clinical image. (**b**) Color Doppler ultrasound (longitudinal view) shows an oval-shaped, anechoic, and avascular structure with internal echoes in the proximal part of the nail bed. This structure produces a posterior acoustic reinforcement artifact typical of fluid-filled conditions and involves the matrix region. There are vessels (in colors) in the proximal nail fold at the periphery of the cyst. No connection was found between the cyst and the distal interphalangeal joint

Malignant Tumors of the Nail

Squamous Cell Carcinomas

These malignant tumors appear on ultrasound as ill-defined and eccentric hypoechoic and heterogeneous structures that commonly erode the nail plate and the bony margin of the distal phalanx as well as affect the lateral nail fold. On color Doppler, there is hypervascularity of the nail bed in the site of the tumor (Fig. 18.25) [17, 18].

Subungual Melanomas

The detection of pigments such as melanin is one of the limitations of ultrasound; nevertheless, it is possible to detect a mass-like structure [42]. According to the degree of invasion, subungual

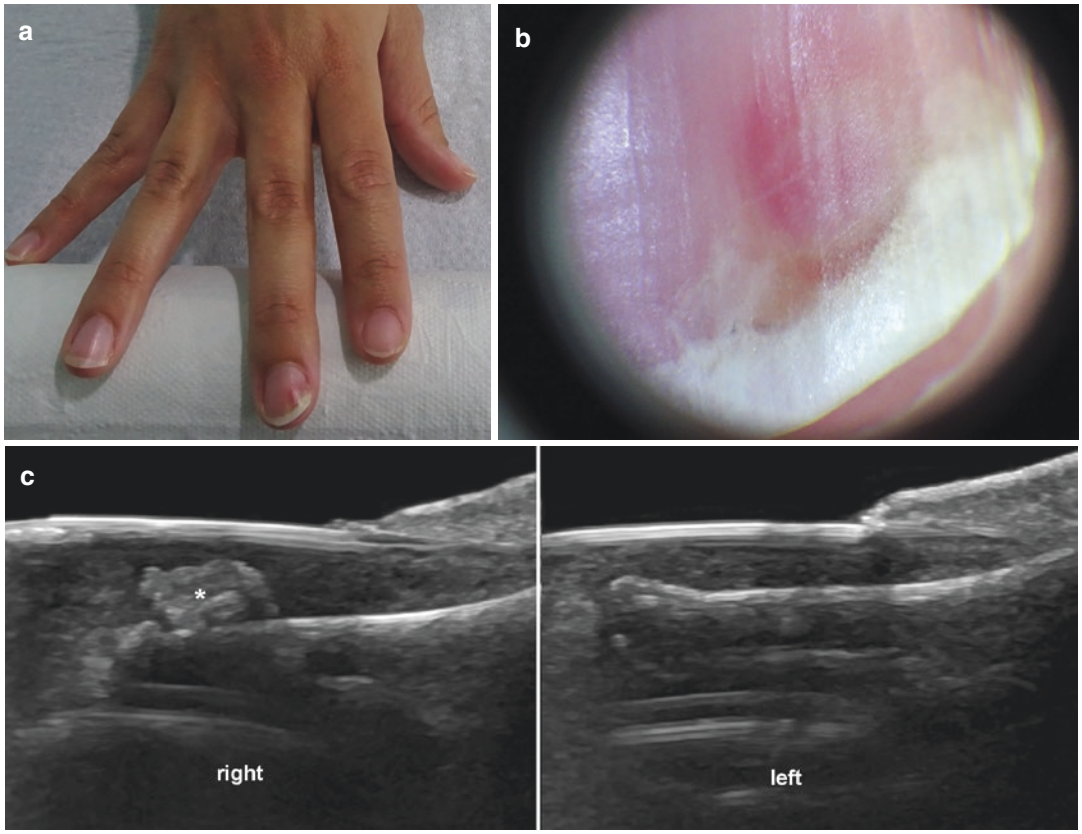

Fig. 18.23 (**a**–**c**) Subungual exostosis (right middle finger). (**a**) Clinical photograph. (**b**) Dermoscopy. (**c**) Grayscale ultrasound image (side-by-side; right versus left) presents hyperechoic band (*) protruding into the nail bed at the right side

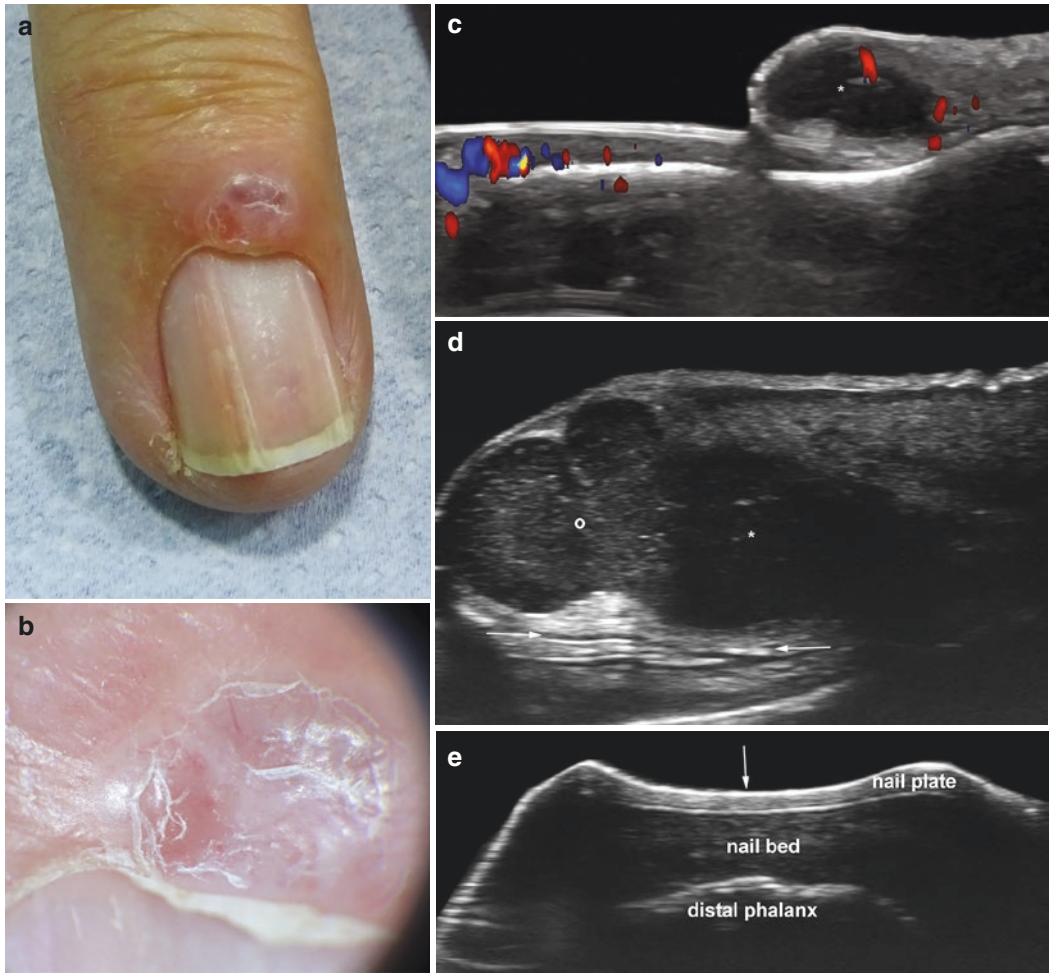

Fig. 18.24 (**a**–**e**) Myxoid cyst (right ring finger)**.** (**a**) Clinical photograph. (**b**) Dermoscopy. (**c**, **d** and **e**) Ultrasound images (**c** and **d**, longitudinal views; **d**, transverse view; **c**, color Doppler, **d** and **e**, grayscale; **c**, at 18 MHz, **d** and **e**, at 70 MHz) show oval-shaped, slightly lobulated structure (*) with mixed echogenicity and posterior acoustic reinforcement artifact (horizontal arrows in **d**), typically seen in fluid-filled entities. Notice the echoes within this structure in **d** (o) and the concavity (vertical arrow pointing down) of the nail plate in **e**

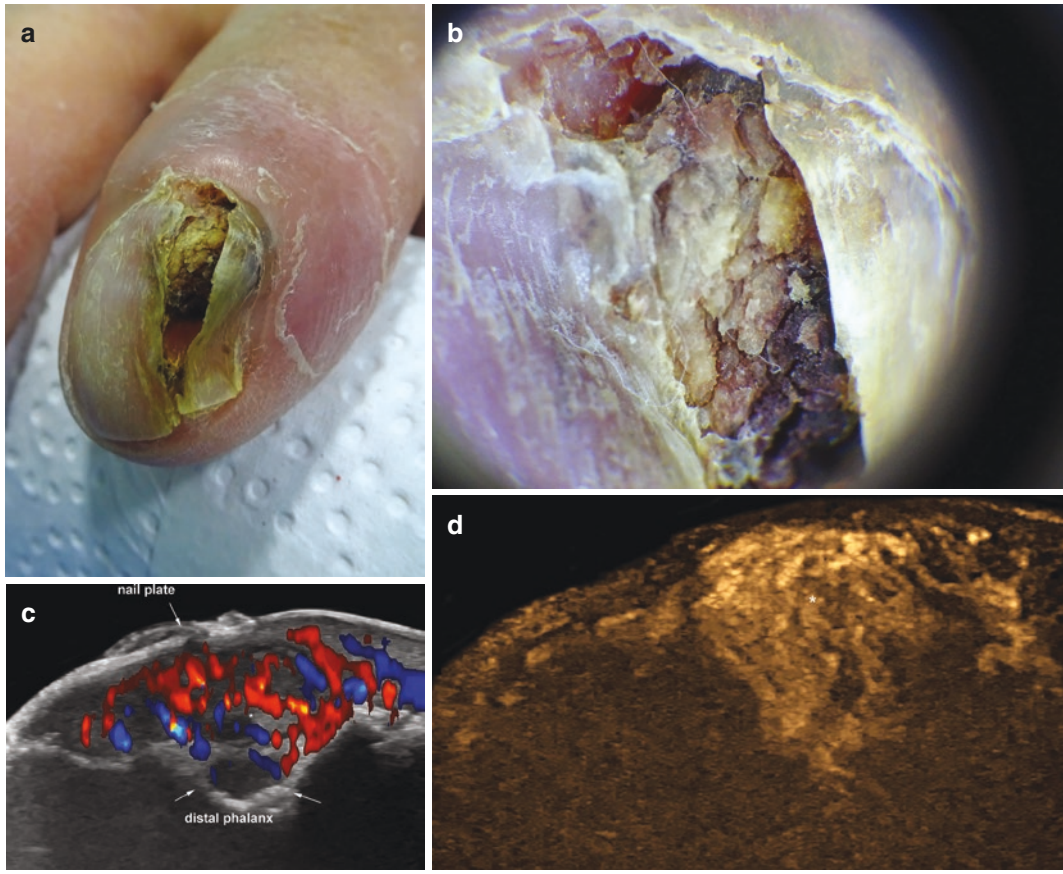

Fig. 18.25 (**a**–**d**) Subungual squamous cell carcinoma (right index finger). (**a**) Clinical photograph. (**b**) Dermoscopy. (**c**) Color Doppler and **b**. Echoangio image (B-Flow, General Electric Health Systems, Waukesha, WI) presents an ill-defined hypoechoic and hypervascular structure (*) that involves the nail bed and erodes the bony margin of the distal phalanx (arrows in **c**). There are upward displacement and irregular contour of the nail plate (**c**). Notice the prominent hypervascularity with chaotic distribution (*) in **d**

melanomas can show as an asymmetric site of hypervascularity without a perceptible mass (Fig. 18.26), or as an ill-defined hypoechoic and hypervascular subungual mass that erodes the nail plate and the bony margin of the distal phalanx [17, 18]. Occasionally, subungual telangiectatic granulomas can mimic melanomas [43]. In congenital melanonychias, there is no subungual hypervascularity [17, 18].

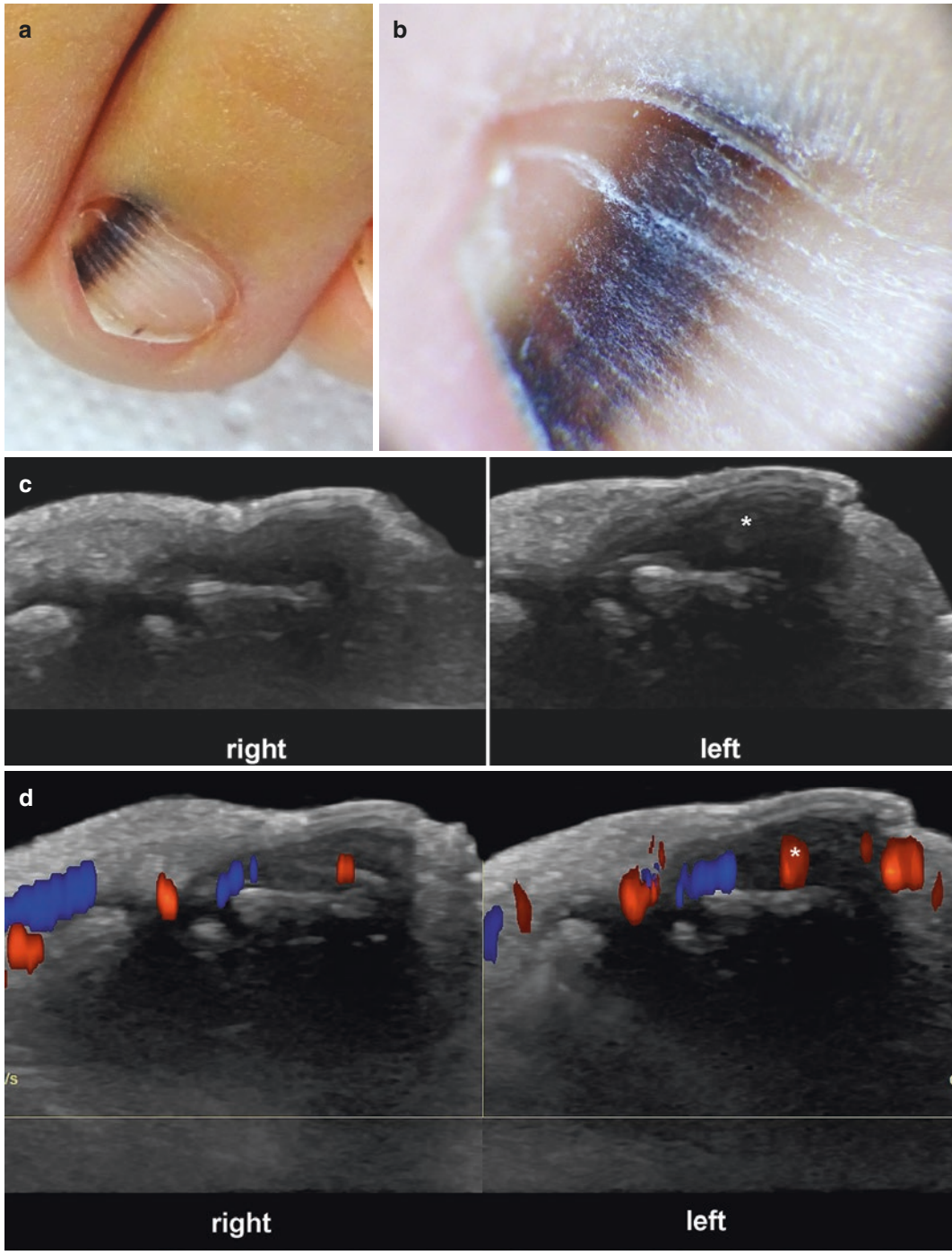

Fig. 18.26 (**a**–**d**) Subungual melanoma (left third toe). (**a**) Clinical image. (**b**) Dermoscopy. (**c**) Grayscale and (**d**) Color Doppler ultrasound (side-by-side comparative views) demonstrate thickening and hypervascularity of the nail bed with thickening of the nail plate on the left side*. No signs of erosion of the bony margin were detected

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19 Onychomycosis: Usefulness of Histomycology

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Abbreviations

KOH Potassium hydroxide mounts
PAS Periodic acid–Schiff

Introduction

Onychomycosis represents 50% of nail diseases and 30% of superficial mycoses. A large proportion of onychomycoses are caused by dermatophytes, predominantly from the genus *Trichophyton*, although nondermatophyte molds and yeasts can also be responsible [1].

Mycological assessments designed to confirm the diagnosis should be performed before treatment [1, 2]. Identification of the exact pathogen(s) involved is crucial because some fungi, particularly yeasts and nondermatophyte molds, are less sensitive or even unresponsive to some antifungal drugs [1]. Conventional diagnosis is based on direct microscopy (potassium hydroxide (KOH) mounts) of clinical specimens, followed by culture and morphological identification of the fungus [3]. Direct microscopy requires experienced investigators to identify the fungal elements and nonetheless produces false-negative results in 5–15% of cases [4]. On the other hand, various structures, such as fibers, air bubbles, and fat droplets, may resemble fungal cells in KOH preparations and thereby may lead to false-positive results [1–4]. In addition, fungi are modular organisms that can leave visible but nonviable segments observable under direct microscopy. This phenomenon leads to KOH-positive but culture-negative samples. Conversely, subungual scraping samples may yield a few viable organisms that can be overlooked in direct microscopy, but grow in culture, giving a KOH-negative but culture-positive sample [4–6]. Fungal culture is a time-consuming procedure and has a high percentage of false-negatives (30–50%) [3–6]. Additionally, the diagnostic accuracy of culture methods ranges from 50% to 70%, depending on how the samples are collected and prepared [7]. Furthermore, apart from correct nail sampling, the successful culture of an infectious agent requires selecting the adequate culture medium, optimal temperature conditions, sufficiently large samples of the nail material, and the presence of viable fungi [8, 9]. Possible contamination with some bacteria or

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nondermatophyte molds can prevent the growth of the actual infectious agent or mask its presence in the case of contaminant overgrowth. Finally, culture methods do not allow the reliable differentiation between pathogenic fungi that have invaded the nail and nonpathogenic secondary colonizers or contaminants [10].

The limited dependability of these conventional detection methods is due to the numerous sources of error that can be involved. Therefore, more rapid and sensitive method is needed. Histopathological examination appears to be a promising method to improve and enhance diagnostic efficiency [11]. It has shown high sensitivity compared with direct microscopy KOH or fungal culture in multiple studies [7]. Before detailing the advantages and disadvantages of this method, we describe the procedure below.

Procedure

Histopathological examination or histomycology is the microscopic examination of histological sections of nail material after histopathological staining of fungal polysaccharides on a nail plate biopsy specimen to reveal the presence of fungi [11–13]. It is essential to take as much of the subungual keratotic debris as possible as this is the site where most fungi are seen. The clipping technique is simple and painless. With the help of a nipper, a fragment of adequate size (at least 4 mm) of the affected nail is cut [9] (Fig. 19.1).

Histomycology requires that the nail specimen be fixed, dehydrated, embedded in paraffin, and sectioned prior to staining. After cleaning the nail in question with an alcohol swab to remove contaminants, the sample is taken using a nail clipper to remove as proximally as possible the full thickness of the nail plate and, if easily accessible, the hyperkeratotic nail bed. The taken specimen is sent to the histopathology lab in an envelope or in a dry container or placed in a formaldehyde solution.

Fig. 19.1 Nail clipping for histomycological examination

The nail clippings are initially softened with softening agents for 24 to 48 hours, then fixed in formalin and dehydrated, embedded in paraffin, cut with a microtome into thin slices of 4 μm, and stained with periodic acid–Schiff (PAS) stain. The most commonly used softening methods are Mollifex Gurr (VWR Int. Ltd.), 10% KOH, and 10% potassium thioglycolate. To enhance adherence of the nail plates to the glass slides, gelatin-coated slides or plastic embedding can be used. An albumin solution with glycerin can be used to prevent the section from sliding off the slides. Altogether, the procedure requires approximately 48 hours to complete.

When evaluating onychomycosis with on a PAS-stained specimen, the fungal hyphae are usually present in the ventral nail plate or in the subungual hyperkeratosis [11, 12]. One study showed that examining the subungual hyperkeratosis resulted in the diagnosis of onychomycosis in 97% of the cases, suggesting that nail plates themselves need to be processed in only 3% of the cases [14].

Interpretation

Staining a portion of the nail plate may allow the identification of the type of fungal structure (hyphae, pseudohyphae, spores, and yeast) and the degree of invasiveness [11, 12, 14]. Several types of stain can be used, with PAS being the most common. Alternative stains to PAS are Grocott methenamine silver, Fontana–Masson, immunofluorescence, and Mayer's mucicarmine. PAS and Grocott methenamine silver stain showed similar sensitivities.

In PAS, the periodic acid oxidizes the hydroxyl groups of the polysaccharides in the fungal cell wall into aldehyde, which then reacts with the Schiff reagent. The fungal elements stained in red [11, 12].

For Grocott methenamine silver staining, chromic acid oxidizes the polysaccharides in the fungal cell wall to aldehydes, and methenamine silver nitrate is then reduced to metallic silver. The background is pale green and the fungal elements are dark brown.

Histologic sections of nail clippings can confirm the diagnosis of onychomycosis, may suggest the nature of the infecting agent (dermatophyte, yeast, molds), and can specify the degree of nail plate invasion [6]. In subungual onychomycosis, the mycelial filaments are located in the subungual keratin and involve the ventral nail plate. In superficial onychomycosis, they are usually restricted to the superficial part of the nail plate; in total onychomycosis, the hyphae invade the whole nail plate and subungual keratin.

Microscopic observation of the samples provides additional information. In general, in cases of invasion by dermatophytes (Figs. 19.2 and 19.3), the mycelial filaments are quite long, rectilinear, and most often oriented parallel to the surface of the nail. Their size is generally regular and PAS staining is uniform. In contrast, invasion by yeast shows short and more or less septate pseudo-

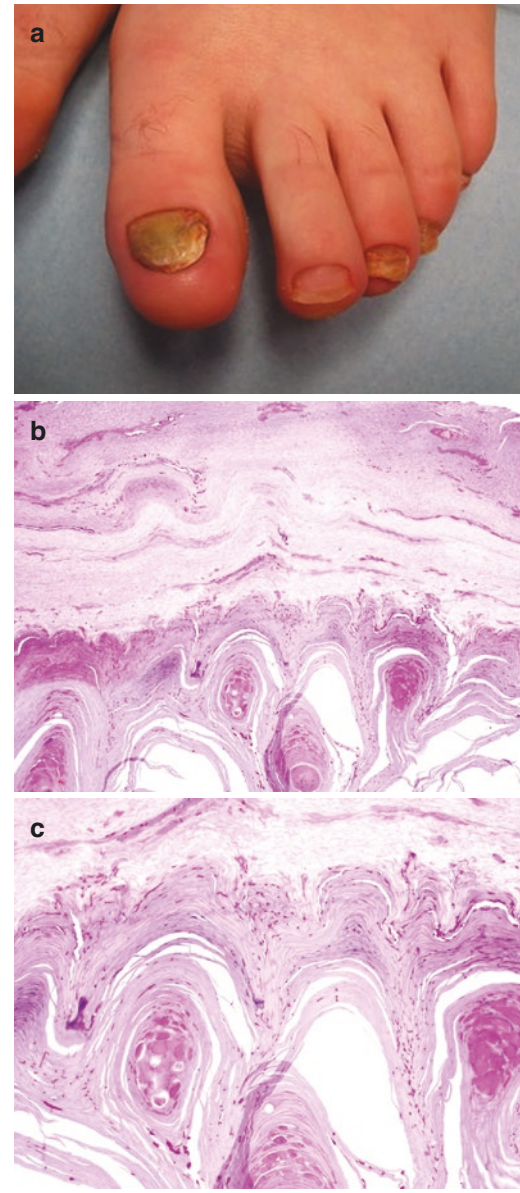

Fig. 19.2 Dermatophytic onychomycosis [*Trichophyton rubrum*] (**a**). (**b**) Regular and eosinophilic hyphae, distributed in the subungual hyperkeratosis [dermatophytes] (PAS, 100x). (**c**) Parakeratosis and regular eosinophilic hyphae, spread in the nail plate and subungual material (PAS, 200x)

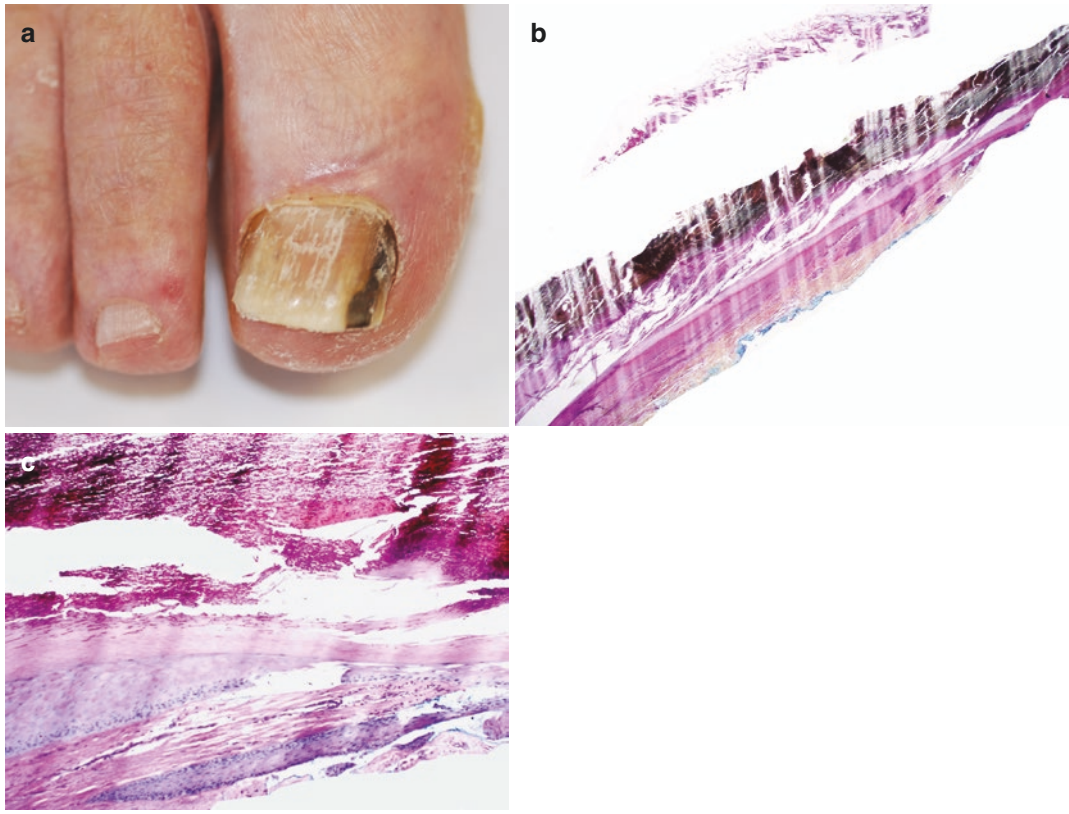

Fig. 19.3 Dermatophytoma (Coll Dr. Giuseppe Cannata). (**a**) Total dystrophic onychomycosis with yellow bands. (**b**) Dense mass involving the nail plate (HES, 40x). (**c**) A high-power view demonstrates PAS-positive branching hyphae invading the nail plate and forming a dense mass (PAS, 200x)

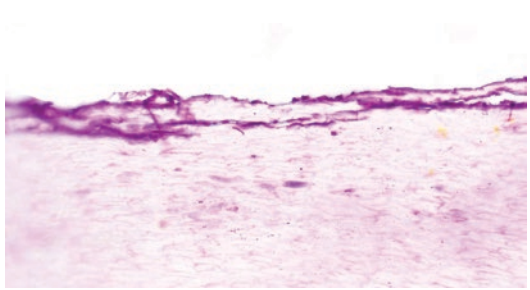

Fig. 19.4 Mold onychomycosis [*Fusarium*]. Truncated spores with thin perforating hyphae invading the ventral part of the nail plate in (PAS x 400)

mycelia, as well as budding blastospores. Truncated spores and irregular hyphae from which thin perforating filaments arise are diagnosed as a mold infection (Fig. 19.4). Sometimes, more specific structures can be observed, such as an aspergillary head, or spores with a hot air balloon-like shape, characteristic of *Scopulariopsis brevicaulis*. The presence of spores without pseudohyphae does not allow a diagnosis of onychomycosis because they can be contaminants. In samples collected after the commencement of treatment, fungal hyphae are paler and more difficult to detect.

Advantages

Histomycology on nail clippings is the most sensitive technique to diagnose onychomycosis, compared with direct microscopy (KOH mounts) and fungal culture [1]. PAS-stained nail plates have the highest sensitivity of the three methods (75–80%), and the turnaround time is limited to 2–7 days [4–7]. A recent meta-analysis [7] evaluating the diagnostic validity, performance, and accuracy of culture, direct microscopic examina-

tion, and PAS staining (biopsy) of nail clippings for onychomycosis gives sensitivity values between 23% and 84.6% [6, 7] for culture, between 44% and 100% for direct microscopy [7, 10, 15], and between 81% and 91.6% for biopsy [7, 10, 15]. PAS-stained biopsies have shown a sensitivity of 100% in some studies [7]. The sensitivity values reported for method combinations are 57% for biopsy combined with direct microscopy [6] and 98.3% for biopsy combined with culture [11]. In addition to high sensitivity, PAS staining results are available quickly, usually within 24 to 48 hours.

For the detection of fungal elements (hyphae) in nail specimens, one study of 631 nail samples showed that PAS staining is the single method with the highest sensitivity with 82% sensitivity, followed by culture (53%) and direct microscopy (48%) [16]. In 64 cases in which a prediagnostic antimycotic treatment had been initiated, PAS staining had by far the highest sensitivity (88%) in comparison with culture (33%) or direct microscopy (50%). Therefore, especially in cases with prior antifungal treatment, histological analysis of PAS-stained nail clippings should be considered as an appropriate diagnostic tool [16].

Many studies advocate combining direct microscopy (KOH mounts) and PAS staining methods to decrease the false-negative rate. Direct microscopy (KOH mounts) combined with mycological culture produces sensitivities between 74% and 78%. Direct microscopy (KOH mounts) combined with histomycology gives sensitivities between 89% and 97%. Combining mycological culture with histomycology gives the highest sensitivity, with rates of 93–96% [7, 16].

Histopathological examination using PAS is easy to perform. The location of the fungus also can be determined with precision. Invading fungi thus can be distinguished from colonizing or contaminating agents [17]. In addition, histomycology can also be used as a simple test to evaluate the effectiveness of the prescribed mycological treatment. It is the most sensitive method for detecting residual infection after therapy with oral antifungal medication [16].

The morphological aspect of the fungus can, in some instances, distinguish dermatophytes from yeasts and nondermatophyte molds. These morphological differences can help identify mixed infections involving more than one fungus [5, 11, 12]. There are two types of mixed infections, according to the presence of fungi at the same site or at different sites of the nail plate. In the first instance, one of the fungal species may represent a passive bystander or an opportunistic agent. In the second case, both fungal species are primary invaders and pathogens.

PAS staining may allow spores, hyphae, pseudohyphae, and yeast to be visualized [11, 12]. Some aspects revealed by histomycology can be interpreted as prognostic factors for the evolution of the onychomycosis under consideration. Furthermore, if the nail dystrophy is not a result of a fungal infection, histology can help diagnose alternative causes, such as psoriasis or hematoma. Finally, the histopathologic slides can be stored and re-evaluated when needed.

No other laboratory method provides similar information.

Disadvantages

Histomycology requires a specialized histology laboratory with a pathologist skilled in interpreting nail pathologies. Furthermore, the cost associated with PAS is often higher than direct microscopy. However, like direct microscopy/KOH testing, the main disadvantages of PAS staining are that the specific causative agent cannot be identified and that viable and nonviable organisms are indistinguishable [4, 7, 10, 15].

Conclusion

Sampling nail specimens is mandatory to confirm diagnosis of onychomycosis before starting treatment, which is lengthy and costly and has potential side effects.

Histomycology on nail clippings is an easy, sensitive, and relatively rapid method to diagnose onychomycosis. The result can be obtained

within about 48 hours, which is relatively quick in comparison with culture methods. Compared with KOH direct microscopy and fungal culture, histomycology is the most sensitive technique. Histomycology is particularly beneficial when the clinical suspicion of onychomycosis has not been confirmed by direct microscopy (KOH testing) or microscopy and culture and, especially, for controlling antifungal treatment courses.

It is also known to be more reliable in determining whether a fungus is invasive or colonizing subungual debris. Investigation of cases with pre-diagnostic antifungal treatment shows another advantage of histomycology. The major disadvantage of the histomycologic method is that it lacks the ability to precisely identify pathogens and their susceptibility profile.

Histomycology appears suitable as a routine diagnostic assay for onychomycosis. It increases the sensitivity in diagnosing onychomycosis beyond that achieved by culture and direct microscopy (KOH testing) alone. Because information concerning the viability of the fungi and accurate identification of the specific pathogen is not available through PAS histology alone, however, culture techniques continue to be necessary in combination with histomycology. When coupled with fungal culture, the overall sensitivity increases to 96% [16].

The combination of direct microscopy and culture is currently the gold standard in the diagnosis of onychomycosis. However, given the inconsistent sensitivity of both of these methods and the potential delay in fungal culture results, histomycological assessment of nail plate specimens is recommended as a complementary, reliable diagnostic tool for difficult cases of onychomycosis [17].

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