Nail is Systemic Disorders: Main Signs and Clues

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KEYWORDS

• Nails • Systemic diseases • Clubbing • Yellow nail syndrome • Scleroderma • Lupus • Connective tissue diseases • Acrokeratosis paraneoplastica

KEY POINTS

- Nail alterations are common in systemic diseases, but most of them are not specific.
- Typical nail signs for systemic disease are rare, but should not be missed.
- Some nail signs should suggest a systemic disease, especially if present on several digits: Beau's lines, onychomadesis, splinter hemorrhages, clubbing, apparent leukonychia, abnormal nail fold capillaries, melanonychia, red lunula and pterygium inversum unguis.

INTRODUCTION

Theoretically, all systemic conditions could result in nail alterations but most of them are reactional and nonspecific but some may be a clue to the diagnosis.

We discuss 9 nail signs that are frequently observed in systemic diseases along with their description and associated diseases. We will then focus on 5 systemic pathologies that could be associated with specific nail changes, hallmarking the condition.

MAIN NAIL SIGNS IN SYSTEMIC DISORDERS

Beau's Lines and Onychomadesis

Beau's lines are transverse superficial grooves of the nail plate. The depression extends across width of the nail and is more visible in the middle part. It is more prominent on the thumb and great toe.[1,2] Beau's lines reflect a transitory damage to the proximal matrix with a decrease in the keratinocyte mitotic activity. The depth of the depression is related to the severity of the matrix injury and the length reflects the duration of the disease. This transverse depression appears 4 to 11 weeks after illness, allowing to date the event.[3] This delay corresponds with the growth of the nail under the proximal nail fold. If it is located on several nails at the same level, a systemic cause is responsible[3] and a thorough history often reveals the culprit (**Box 1**).[1,3]

Onychomadesis corresponds with a complete temporary arrest of the nail production.[2] When the growth restarts, the proximal nail plate will push away the distal part ending with onychoptosis (nail plate shedding) .

Splinter Hemorrhages

Splinter hemorrhages are a frequent but not specific clinical finding.[4,5] Splinter hemorrhages are fine, nonblanchable, red–brown to black longitudinal streaks of 1 to 3 mm visible through the plate, most frequently on its distal third, but they may be seen at any level.[4,6] They are usually asymptomatic and migrate distally with the nail growth.[4,6] Splinter hemorrhages results from bleeding of the nail bed capillaries into the longitudinal ridges of the nail bed.[2] Dermoscopy shows deep red to black lines with typical distal fading of the pigmentation, owing to progressive hemosiderin degradation.[2] Splinter hemorrhages can be idiopathic, traumatic, or associated with a nail tumor or with inflammatory dermatosis.[4,6,7]

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Box 1
Main systemic causes of Beau's lines

Higher fever

Viral diseases in children

- Hand–foot–mouth disease

Cardiovascular disease

Hepatic, pulmonary, endocrine severe disease

Malnutrition and deficiency

Change in pressure or hypoxia

Drugs (antimitotic drugs, chemotherapeutic agents, …)

Data from Rubin A, Holzberg M, Baran R. Physical signs. In: Baran R, de Berker DAR, Holzberg M, et al., editors. Baran and Dawber's Diseases of the Nails and their Management, 5th edition. Oxford: Wiley Blackwell; 2019; and Zaiac MN, Walker A. Nail abnormalities associated with systemic pathologies. Clin Dermatol 2013;31(5):627-49.

In systemic diseases, Splinter hemorrhages involve simultaneously several nails, occur mostly on the proximal third and can be painful.[7] Many systemic diseases have been associated with splinter hemorrhages (**Box 2**)[1,4,7] but they rarely are the only manifestation.[4] If splinter hemorrhages are present in more than 1 fingernail, an in-depth medical history and clinical examination are required and will guide the additional diagnostic testing.[4] Treatment is causative

Lichenoid Alterations

Lichenoid alterations are defined as nail changes resembling or mimicking those of matrix nail lichen planus. These alterations can be seen in different systemic disorders . Nail involvement is rare in systemic amyloidosis, but it can be the initial manifestation and sometimes the only cutaneous sign.[8–10] Nail abnormalities can mimic lichen planus with all the nails showing thinned, brittle, longitudinal ridges, distal fissures, and sometimes trachyonychia.[8–11] Splinter hemorrhages are common. Nail involvement can lead to anonychia. Some reports mention chronic paronychia, onycholysis, and severe subungual hyperkeratosis.[12] A histologic examination shows typical amyloid deposits in the dermis and around the vessels in the nail matrix and/or nail bed. The onychodystrophy usually slowly worsens with the disease duration.[10,11] Nail dystrophy resolution has been reported after a successful treatment of multiple myeloma.[13]

In sarcoidosis, nail involvement is also rare, but it indicates a long-lasting systemic disease.[14,15] It is

Box 2
Systemic causes of splinter hemorrhages

Elderly

Cardiovascular diseases

- *Bacterial endocarditis*
- Congenital heart disease
- Arterial/cholesterol emboli
- Mitral stenosis
- Atrial fibrillation
- Raynaud phenomenon
- Aortic dissection

Hematologic diseases

- Anemia
- Thrombocytopenia, thrombotic thrombocytopenic purpura
- Osler–Weber–Rendu syndrome
- Cryoglobulinemia
- Leukemia
- Hypereosinophilic syndrome

Connective tissue diseases and vasculitis

- *Antiphospholipid syndrome*
- Systemic lupus erythematosus
- Dermatomyositis
- Systemic scleroderma
- Rheumatoid arthritis
- Systemic juvenile idiopathic arthritis
- Medium vessels vasculitis
- Thromboangiitis obliterans
- Granulomatosis with polyangiitis
- Behçet disease

Endocrine diseases

- *Diabetes mellitus*
- Hypoparathyroidism
- Thyroid diseases

Gastrointestinal diseases

- Cirrhosis
- Hepatitis
- Hemochromatosis
- Inflammatory bowel disease

Drugs

- *Tyrosine kinase inhibitors* (sunitinib, sorafenib)
- Anti-vascular endothelial growth factor receptor drugs

Others

- *Chronic renal failure* (hemodialysis or peritoneal dialysis)
- Meningococcemia
- Chronic or acute exposure to high altitude
- Systemic amyloidosis
- Scurvy
- Sarcoidosis
- Sweet's syndrome
- Irradiation

Data from Refs.[1,4,7]

mostly associated with bone alteration of the underlying phalanges. Radiology shows osteolysis with a honeycomb trabecular pattern and radiolucent bone cysts and could help in the diagnosis of nail sarcoidosis. However, nail sarcoidosis without bone involvement and in the absence of any systemic manifestation has been described.[16] Nail manifestations are diverse and related to the presence of noncaseating granulomas in the dermis.[17] A case of isolated hyponychium sarcoidosis[18] and a case with longitudinal erythronychia[19] have been reported. Skin sarcoidosis as lupus pernio and dactylitis can be associated with nail abnormalities, which are a sign of severe disease.[14] Finger clubbing and osteoarthropathy are rarely associated to pulmonary sarcoidosis.[20] Nail disease can be treated with high-potency topical steroids, intralesional steroid injection, or systemic treatment (oral corticosteroids and/or hydroxychloroquine), but with poor effect on the bony alteration.[14–16]

In cutaneous graft-versus-host disease (GVHD), nails are involved in one-third to one-half of the patients.[21–23] In children, nail involvement is related to severe cutaneous GVHD and pterygium is associated with severe lung disease.[22] In adults, nail dystrophy seems to be more related to the duration of the disease[21] (**Fig. 1**). Nail changes are often associated with scleroderma-like or lichenoid cutaneous lesions, but it may be the first manifestation of chronic cutaneous GVHD.[24] Treatment is the same as that for chronic cutaneous GVHD and should involve hematologists. Systemic corticosteroids are of some help.

D congenita is an exceptional heterogenous inherited syndrome related to a defective telomer maintenance, associated with bone marrow failure, premature aging, and cancer predisposition.[25,26] This genetic disorder is characterized by the triad associating nail dystrophy, oral leukoplakia, and reticular pigmentation of the neck or the body.[25,26] Nail alterations are present in 90% of patients, usually before the age of 10 years and affects the fingernails first. Allogenic hematopoietic stem cell transplantation is the only curative treatment for bone marrow failure.[25,26]

Clubbing

Digital clubbing, also known as Hippocratic fingers, is defined by morphologic changes[1]:

- Soft tissue hypertrophy with bulbous enlargement of the distal digit.
- Increased transverse and longitudinal curvature of the nail.

Clubbing can be obvious on clinical examination, but subtle presentations can be missed.[27] Different signs may help to differentiate clubbing from pseudoclubbing[27,28]:

- Lovibond's angle measures the angle between the proximal nail fold and the nail plate on a lateral view. Physiologically the angle is lower than 165° but exceeds 180° in clubbing (**Fig. 2**).[29]
- A positive Schamroth's sign shows an obliteration of the normal rhomboidal space created by placing the dorsal aspects of opposite symmetric terminal phalanxes together in clubbed fingers (**Fig. 3**).[30]
- The ratio of Rice and Rowland is the ratio between the thickness of the middle finger on a lateral view, at the level of the proximal nail fold and the distal interphalangeal joint. If it exceeds 1, clubbing is confirmed (see **Fig. 2**).[31]

Clubbing can be congenital (associated or not with various genetic syndromes) or acquired and unilateral or bilateral.[27,28] It can be isolated or occur as part of the hypertrophic osteoarthropathy syndrome, characterized by periostosis of long bones, arthralgia, and clubbing.[27,28] This syndrome can be primary (also known as pachydermoperiostosis, an autosomal-dominant disorder) or secondary. Clubbing is more frequent in the hands, but can also be seen in the feet. The evolution is slow without pain, but stiffness and discomfort can occur. Interestingly, many patients do not notice the clubbing.[27] Secondary hypertrophic osteoarthropathy syndrome and clubbing can be associated with many different diseases, particularly neoplastic, pulmonary, digestive, or cardiac pathologies (**Boxes 3** and **4**).[1,27,28] Secondary hypertrophic osteoarthropathy syndrome is more often paraneoplastic, with 90% of adults who have or will develop neoplasia (especially

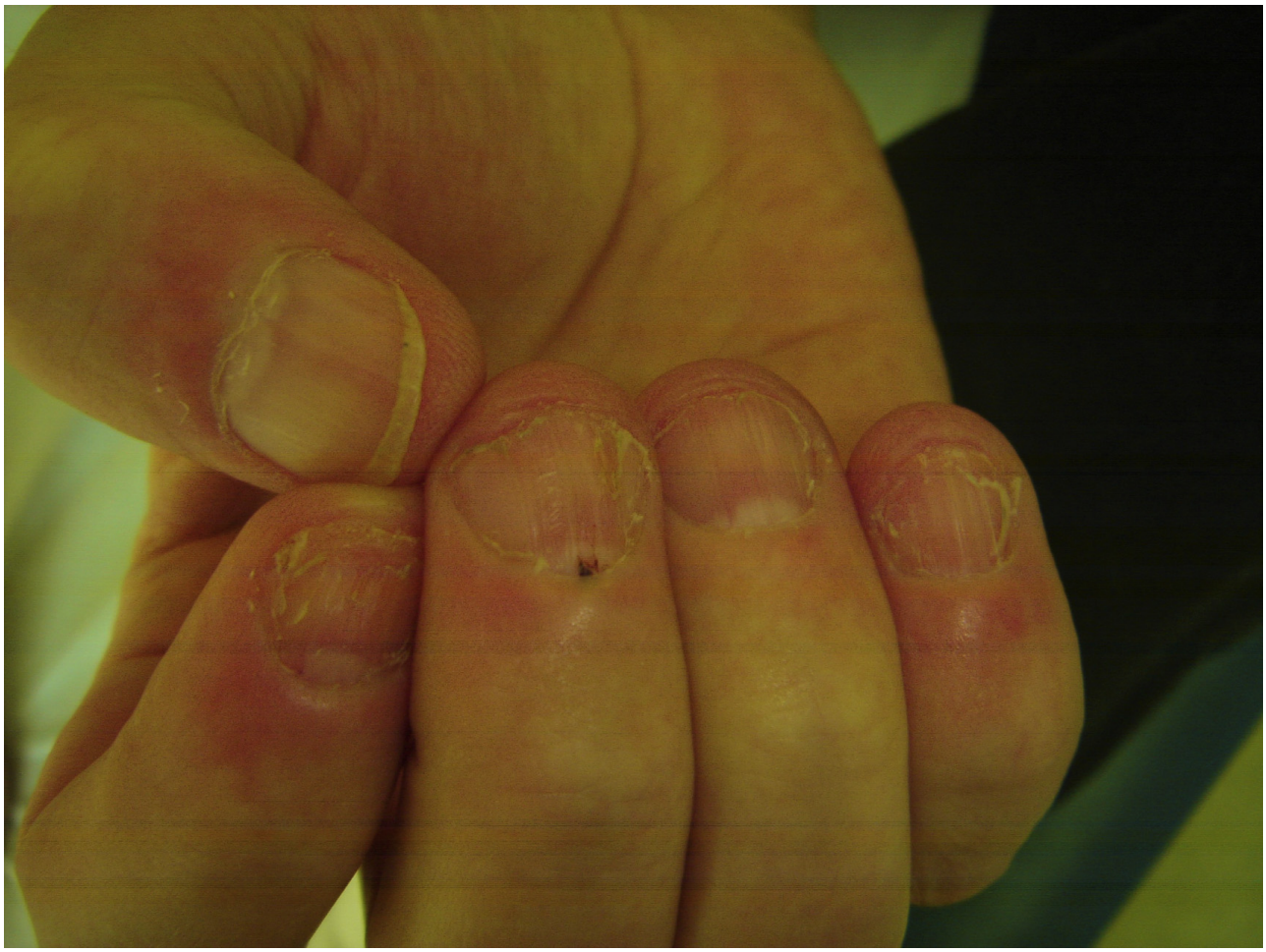

Fig. 1. Lichenoid alterations with nail thinning, longitudinal ridging and fissuring in cutaneous GVHD.

pulmonary malignancy with non-small cell lung carcinoma).[32] Pathogenesis remains unclear although several hypotheses have been proposed.[27,28] Currently, the most accepted hypothesis is an abnormal expression of fibroblast growth factors.[33] This overexpression is induced by different pathogenetic mechanisms, according to the underlying disease, leading to a common final pathway: the production of vascular endothelial growth factor and platelet-derived growth factor.[27,28,33] Vascular endothelial growth factor and platelet-derived growth factor promote synergistically edema, vascular hyperplasia, fibroblast proliferation, collagen synthesis, and new bone formation, all symptoms observed in clubbing or hypertrophic osteoarthropathy syndrome.[33]

Acquired clubbing requires a complete work-up looking for the cause.[27,28]

- In acquired unilateral clubbing
  - Complete history and clinical examination
  - Angiography
- In acquired bilateral clubbing
  - Complete history and clinical examination
  - If no relevant symptoms or signs: chest radiography
  - Work-up and specialist referral according to symptoms/signs[27,28]
- In acquired bilateral hypertrophic osteoarthropathy syndrome or clubbing with joint pain: more aggressive screening for malignancy need to be done considering the higher association with malignancy

Finally, clubbing can be idiopathic, but this is an exclusion diagnosis.[27,28,34] Patient reassurance is mandatory after a complete negative work-up, but ensure that the patient has the regular cancer screenings.[27,28,34]

The treatment of secondary clubbing or hypertrophic osteoarthropathy syndrome is the treatment of the underlying cause.[27,28,35] In case of painful hypertrophic osteoarthropathy syndrome, selective cyclo-oxygenase-2 inhibitors, bisphosphonates, or octreotide can alleviate symptoms.[35]

Leukonychia

The term leukonychia (LK) describes white nails. It can be divided into 3 subtypes[1]:

1. True LK, with nail plate alteration, originating from altered keratinization in the distal matrix;

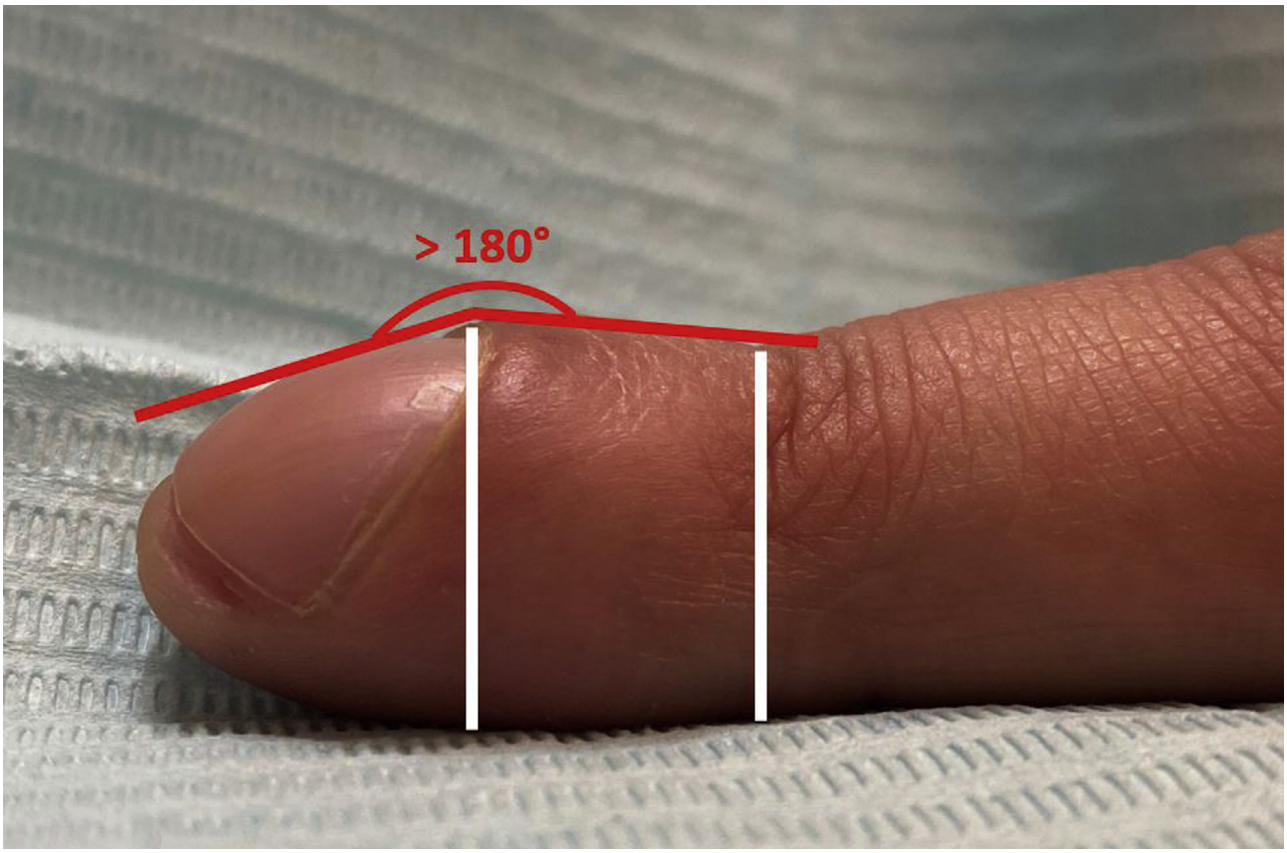

Fig. 2. Lovibond's angle (*red*) and the ratio of Rice and Rowland (*white*) in clubbing.

2. Apparent LK, with involvement of the subungual tissue, through a normal nail plate; and
3. Pseudo-LK, with nail plate alteration, not related to the matrix but external factors.

True LK can be totalis, partialis, striata, or punctate. In this rare condition, the nail seems to be opaque milky to bulky white. The LK does not fade with pressure and moves distally with the nail growth.[1,3]

LK can be traumatic, inherited (related or not to genetic syndrome), or associated to a systemic condition. The historical Mee's lines are due to arsenic intoxication and present as 2 transverse bands of 1 to 2 mm wide, parallel to the lunula, located on the same level of several nails.[1] Other intoxications like thallium, selenium and fluorine as well as other conditions like trauma and drugs (chemotherapy) may also induce transverse white lines. They should not however be called Mee's line, which refers only to arsenic intoxication.[36] Many drugs and chemical are accumulated and stored in nails, reflecting an exposure period of several months. Toenails are used as exposure biomarkers in environmental and forensic medicine.[37]

Apparent LK is the main type observed in systemic diseases. It presents as a white

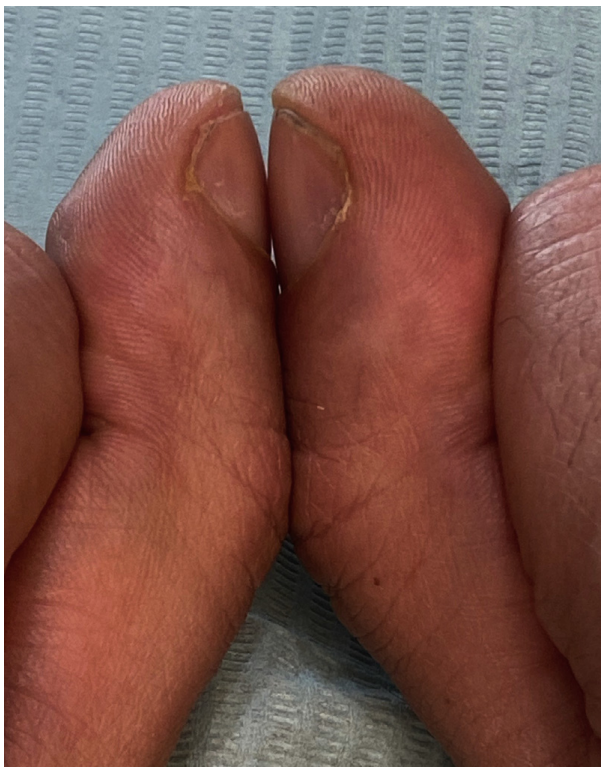

Fig. 3. A positive Schamroth's sign in clubbing, showing an obliteration of the normal rhomboidal space.

Box 3
Diseases associated with unilateral clubbing

Neurologic

- Hemiplegia

Vascular

- Aneurysm
- Dialysis fistula
- Infected arterial graft
- Takayasu's arteritis

Data from Refs.[1,27,28]

discoloration of the plate related to bed alterations, mainly abnormal vascularization, through a normal translucent nail plate. Typically, it fades with pressure and does not migrate with nail growth.[1,3] Apparent LK can be seen in healthy individuals, but it might be the sign of an underlying systemic disease.

Four types of apparent leukonychia

Terry's nails The LK involves the whole nail except the last distal 0.5 to 3.0 mm forming a pink to brownish distal band on the free edge. The lunula may or may not be visible. Usually, all the fingernails are involved but this condition is more pronounced on the first and second fingers.[38] Different associations have been reported (**Box 5**)[1,3,38–41] but liver cirrhosis is the most common (in up to 82%).[38,39,42]

Half and half nails, also called Lindsay's nails The LK involves the proximal part of the nail bed and a distal pink, red to brownish area involving 20% to 60% of the total length. The 2 parts are separated transversely by a well-defined line.[43,44] Half and half nails were first described in chronic kidney disease and are present in approximatively one-third of patients on hemodialysis.[43] The relation between half and half nails and hemodialysis remains controversial. For some authors, half and half nails is related to the long-term uremia and not to the dialysis itself.[45,46] This apparent LK could disappear after kidney transplantation.[45] Other associations are cited in **Box 6**.[3,20,41]

Muehrcke's lines These transverse white bands parallel to the lunula, are most prominent on the second, third, and fourth fingernails, and rarely observed on the thumbs.[47] The first association described and one of the main causes of Muehrcke's lines is hypoalbuminemia (albumin <2.2 g/dL). Typically, Muehrcke's lines disappear when the albumin levels return to normal and

Box 4
Systemic diseases associated with bilateral clubbing

Malignancy

- ***Non-small cell lung carcinoma***
- ***Bronchogenic carcinoma***
- Mesothelioma
- Lymphoma
- Nasopharyngeal carcinoma
- Pulmonary metastases
- Esophageal carcinoma
- Gastric adenocarcinoma
- Renal cell carcinoma
- Thyroid cancer

Pulmonary diseases

- ***Bronchiectasis***
- ***Chronic obstructive pulmonary disease***
- ***Idiopathic fibrosis***
- ***Pulmonary arteriovenous malformations***
- ***Hepatopulmonary syndrome***
- Asbestosis
- Cystic fibrosis
- Sarcoidosis
- Extrinsic allergic alveolitis
- Emphysema
- Tuberculosis
- Pleural empyema
- Pulmonary abscess

Cardiovascular diseases

- ***Cyanotic heart disease***
- Congestive heart failure
- Endocarditis
- Aortic aneurysm
- Atrial myxoma

Gastrointestinal diseases

- ***Crohn's disease***
- ***Cirrhosis (biliary and alcoholic)***
- ***Chronic hepatitis***
- Ulcerative colitis
- Chronic parasitic infections
- Malabsorption syndromes

Endocrine diseases

- Grave's disease
- Secondary hyperparathyroidism

Systemic diseases

- Systemic lupus erythematous

Others

- Human immunodeficiency virus
- Syphilis
- Polyneuropathy, organomegaly, endocrinopathy, monoclonal protein, skin changes (POEMS) syndrome

Data from Refs.[1,27,28]

comes back if they decrease again.[47,48] However, we can see Muehrcke's lines in patients with normal albuminemia[48] (**Box 7**).[3,20,41,48]

Neapolitan nails Neapolitan nails are characterized by a loss of the lunula and 3 transverse bands: the proximal one with apparent leukonychia, a normal pink band, and a distal opaque band at the free edge of the nail.[20,49] It is present in 20% of patients older than 70 years and should not be misinterpreted as Terry or Lindsay's nails. Neapolitan nails are also described in patients with hemiplegia[50]

Nail Fold Capillaries

The microvasculature is easily seen in the proximal nailfold because the dermal capillary loops are horizontal and run parallel to the skin surface, visible throughout their length. The nailfold capillary network can be evaluated by microscopy (called nailfold capillaroscopy), nailfold videocapillaroscopy, and dermoscopy.[51]

The dermoscope is helpful for the identification of major qualitative abnormalities, such as giant capillaries.[52] However, nailfold capillaroscopy and nailfold videocapillaroscopy offer a more detailed imaging with a semiquantitative approach and cannot be replaced by dermoscopy.[53] To have a complete interpretation of images, nailfold capillaroscopy is performed on all fingers, except the thumb.[53,54]

Through (semi)-quantitative and qualitative assessment, a normal capillaroscopy can be distinguished from an abnormal one.[55,56] A normal capillary looks like a thin, regular hairpin, with an afferent, transitional, and efferent limb.[51,53] Normal capillaries are homogeneously sized and regularly arranged in a parallel fashion. Nevertheless, there can be subtle morphologic variations or even nonspecific abnormalities of capillaroscopic characteristics[51,55] (**Fig. 4**).

In systemic sclerosis (SSc) and diseases of the scleroderma spectrum (mixed connective tissue disease, dermatomyositis, undifferentiated connective tissue disorders), specific (pathognomonic) abnormalities or a pathognomonic combination of specific anomalies occur: giant capillaries, hemorrhages, loss of capillaries and abnormal shapes (ie, "neoangiogenesis"). These pathognomonic abnormalities form the scleroderma pattern. This scleroderma pattern is found in 86% to 100% of patients with SSc, but also in 30% to 75% of patients with dermatomyositis, in 50% to 65% of patients with mixed connective tissue disease, and in 14% of patients with undifferentiated connective tissue disorders.[53]

Recently, a fast track algorithm has been proposed and validated multicentrally which allows capillaroscopists with any level of experience to correctly classify images as nonscleroderma pattern or scleroderma pattern.[57] This algorithm relies on 3 rules[57]:

1. The presence of 7 or more capillaries AND the absence of giant capillaries allows to call the capillaroscopic image a nonscleroderma pattern. This comprises perfectly normal

Box 5
Diseases associated with Terry's nails

Age

Liver cirrhosis

Congestive heart failure

Diabetes mellitus

Infectious

- Human immunodeficiency virus/AIDS
- Leprosy
- Tuberculosis

Hematological disorders

Chronic renal failure

Neoplastic (pancreatic carcinoma, plasmacytoma)

Rheumatologic

- Reactive arthritis
- Rheumatoid arthritis
- Systemic sclerosis

Malnutrition

Drugs (cyclophosphamide, itraconazole, vincristine)

Data from Refs.[1,3,38,39,40,41]

Box 6
Diseases associated with half and half nails

Healthy individuals

***Chronic renal disease* with or without hemodialysis**

Cirrhosis

Crohn disease

Behçet disease

Kawasaki disease

Human immunodeficiency virus

Malnutrition

Drugs (androgens, chemotherapeutic agents)

Data from Refs.[3,20,41]

images but also images with nonspecific abnormalities.

2. The presence of giant capillaries or the presence of an extremely lowered capillary density (≤3 capillaries) in combination with abnormal shapes (a late scleroderma pattern) allows the capillaroscopist to call the capillaroscopic image a scleroderma pattern.
3. If the image does not meet rule number 1 or 2, then the image is automatically classified as a nonscleroderma pattern.

There is a dynamic evolution of the microvascular alterations in SSc and 3 progressive patterns have been described to evaluate the level of microangiopathy: early, active, and late scleroderma patterns.[51,58] Giant capillaries are the hallmark of the early and active scleroderma patterns, and a severe loss of capillaries with abnormal shapes characterize the late pattern.[51,57,58]

Nailfold capillaroscopy is mainly indicated in diagnosing connective tissue diseases associated with a prominent microangiopathy.[51] It can differentiate primary from secondary Raynaud phenomenon. Also, it is useful in diagnosing early SSc and scleroderma spectrum diseases.[51,53] Beside its diagnostic purposes, nailfold capillaroscopy also has a prognostic value.[51,53]

Box 7
Diseases associated with Muehrcke's lines

Hypoalbuminemia

- Nephrotic syndrome, glomerulonephritis
- Liver cirrhosis, others hepatic diseases
- Malnutrition
- High altitude

Chemotherapeutic agents

Heart transplantation

Data from Refs.[3,20,41,48]

- The Raynaud phenomenon can be the first sign of scleroderma spectrum disease. Nailfold capillaroscopy and antinuclear antibodies, together with a complete medical history and physical examination, are part of the initial mandatory work-up to differentiate primary from secondary Raynaud phenomenon. Giant capillaries are the most striking feature of Raynaud phenomenon secondary to scleroderma spectrum diseases.[51] The risk of developing SSc in patients with Raynaud phenomenon, is up to 65% in 5 years if patients have both specific positive antinuclear antibodies and a scleroderma pattern on nailfold capillaroscopy.[53,59] A regular follow-up is mandatory.
- In SSc, nailfold capillaroscopy allows an early diagnosis and is now considered as a major diagnostic criterium[60] and moreover has a prognostic interest. It evaluates the severity of SSc and helps to identify patients at risk of visceral involvement. The evolution of nailfold capillaroscopy images to a late pattern is associated with a higher modified Rodnan skin score, with an increased risk of pulmonary arterial hypertension, interstitial lung disease, cardiac and vascular pathology, and an increased mortality.[51,53] Patients with SSc with a nonscleroderma pattern have less severe skin and pulmonary involvement.[61] Some studies have described an improvement in nailfold capillaroscopy abnormalities under systemic treatment.[62,63]
- In dermatomyositis, the scleroderma-like pattern is observed with usually a more anarchic picture with a higher capillary density (no capillary dropout), more neo-formed capillaries (ramified capillaries) and capillary disorganisation.[64] Some authors report a normalization of the nailfold capillaries under immunosuppressive treatment, especially rituximab.[65]
- In the others autoimmune disease, nailfold capillaroscopy is less specific and is not paramount in the diagnosis.[51] For systemic lupus erythematosus, there is no specific capillaroscopic pattern but tortuous capillaries, hemorrhages and abnormal morphology are more prevalent than in the normal

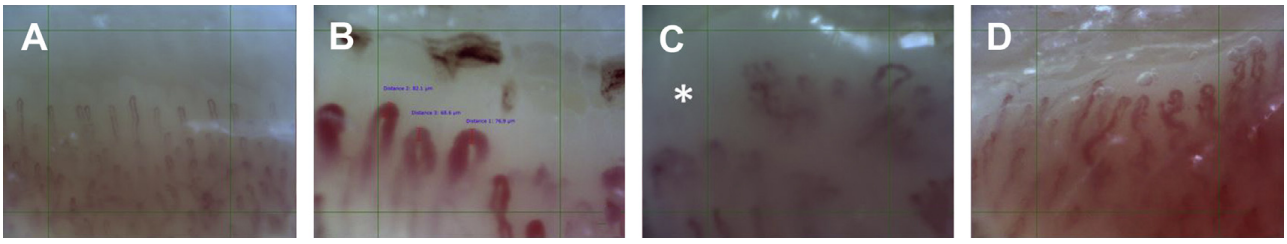

Fig. 4. Normal capillaroscopy image with thin regular hairpin loops with a homogeneous distribution (*A*), an active scleroderma pattern with giant capillaries and hemorrhages (*B*), a late scleroderma pattern with avascular areas (*asterisk*), abnormal capillary shapes (*C*), and tortuous capillaries in systemic lupus erythematosus (*D*).

population.[56] There is also no specific pattern on nailfold capillaroscopy for rheumatoid arthritis[66]

Melanonychia

Longitudinal melanonychia describes a longitudinal gray to brown–black band extending from the proximal nail fold to the free edge. It corresponds to the presence of melanin within the nail plate resulting from activation or proliferation of matrix melanocytes.[67] Causes of melanonychia are multiple and here will be cited only those related to systemic disorders. Melanonychia can be longitudinal or diffuse. Muehrcke's lines may be associated with endocrinopathies (acromegaly, Addison disease, Cushing syndrome, hyperthyroidism), nutritional deficiencies, infections (eg, human immunodeficiency virus), and connective tissue diseases.[3,68] Many drugs can lead to melanonychia, the main being chemotherapeutic agents (hydroxyurea, doxorubicin, fluorouracil, taxanes, cyclophosphamide); tetracyclines; antiretroviral drugs like nucleotide reverse transcriptase inhibitors and antimalarial agents.[40,41]

Peutz-Jeghers syndrome, a rare genetic autosomal-dominant disease, is characterized by mucocutaneous pigmentation and multiple intestinal polyps associated with an increased risk for

Box 8
Diseases associated with red lunula

Connective tissue diseases

- ***Rheumatoid arthritis***
- ***Systemic lupus erythematosus***
- Dermatomyositis/polymyositis
- Sjögren syndrome
- Polymyalgia rheumatica

Cardiac diseases

- Congestive heart failure
- Myocardial infarction
- Rheumatic heart disease
- Hypertension
- Conduction abnormalities
- Atherosclerotic disease

Hematologic malignancies

Pulmonary diseases

- Chronic obstructive pulmonary
- Chronic bronchitis
- Emphysema

Gastrointestinal diseases

- Hepatic cirrhosis

Renal: proteinuria

Toxicity: alcohol or tobacco use, carbon monoxide poisoning

Drugs: corticosteroids, procainamide

Data from Refs.[1,3,20,72,73,74]

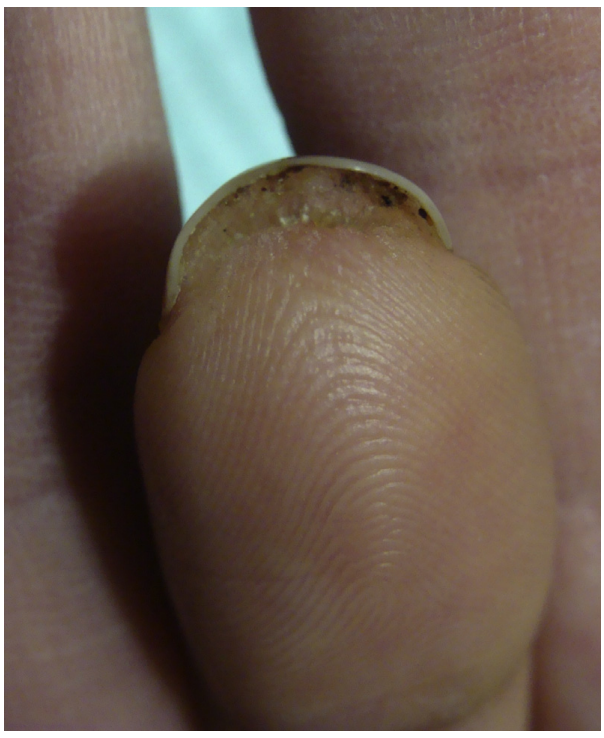

Fig. 5. Pterygium inversum unguis showing an obliteration of the distal nail groove.

malignancies.[69] Brown–blue macules are localized on acral sites particularly the lips, oral mucosa, palms, and soles. Longitudinal melanonychia have been exceptionally described.[69] The main differential diagnosis is the Laugier–Hunzinker–Baran syndrome.[70,71] This syndrome associates lenticular hyperpigmentation of the oral and anogenital mucosal with frequent longitudinal melanonychia without any systemic involvement.[69] Longitudinal melanonychia are present in 60% of the cases, more frequently on the fingernails and pseudo-Hutchinson has been described[69]

Red Lunula

Red lunula is defined by red–pink to dusky redness of the lunula. It can be complete or partial, with persistence of a narrow white band at the distal portion of the lunula. It fades under pressure on the nail plate.[72] All the nails can be affected but red lunula is more frequent on fingernails, especially the thumb where the distal matrix is more visible.[20] Red lunula can be associated with systemic disorders (**Box 8**)[1,3,20,72–74] and be the first sign of the underlying disease.[73] Red lunula can also be seen with medications as amoxicillin/clavulanic acid (fixed drug eruption), corticosteroid and procainamide.[20] The physiopathology of red lunula remains unclear.[72]

Pterygium Inversum Unguis

Pterygium inversum unguis, or ventral pterygium, is the obliteration of the distal groove (**Fig. 5**).[75,76] This adhesion between the hyponychium and the nail plate results in pain or bleeding with minimal trauma or when the nails are trimmed.[75–77] Pterygium inversum unguis involves mainly the fingernails, exceptionally the toenails.[76,77] Pterygium inversum unguis can be congenital, but the majority are acquired (idiopathic or secondary).[76,77] Secondary pterygium inversum unguis most commonly occurs in autoimmune diseases, especially SSc or systemic lupus erythematosus. Caputo and colleagues[77] evaluated that pterygium inversum unguis occurs in 16% of these patients. For this reason, women are more prone to develop a pterygium inversum unguis.[76,77] Other associations are reported in **Box 9**.[1,20,76–79] The physiopathology is not fully understood and could be different according to the etiology.[76] Microvascular ischemic lesions with subsequent scarring are suspected in connective tissue diseases and leprosy.[77–79] There is not treatment for pterygium inversum unguis as it results from scarring. Surgery is not an option in systemic disorders

Box 9
Systemic diseases associated to pterygium inversum unguis

Connective tissue diseases

- ***Systemic sclerosis***
- ***Systemic lupus erythematosus***
- **Dermatomyositis**

Diabetes mellitus

Leprosy

Cerebral vascular accident with hemiparesis (unilateral pterygium inversum unguis)

Drugs: beta-blockers

Data from Refs.[1,20,76,77,78,79]

SELECTED SYSTEMIC DISORDERS WITH NAIL INVOLVEMENT

Gout

Tophi are more frequent in chronic stage but they can also be the first clinical sign of gout.[80] Gouty tophi, pink to whitish firm nodules or swelling, could be periungual with perionychium deformation and Beau's lines or longitudinal groove owing

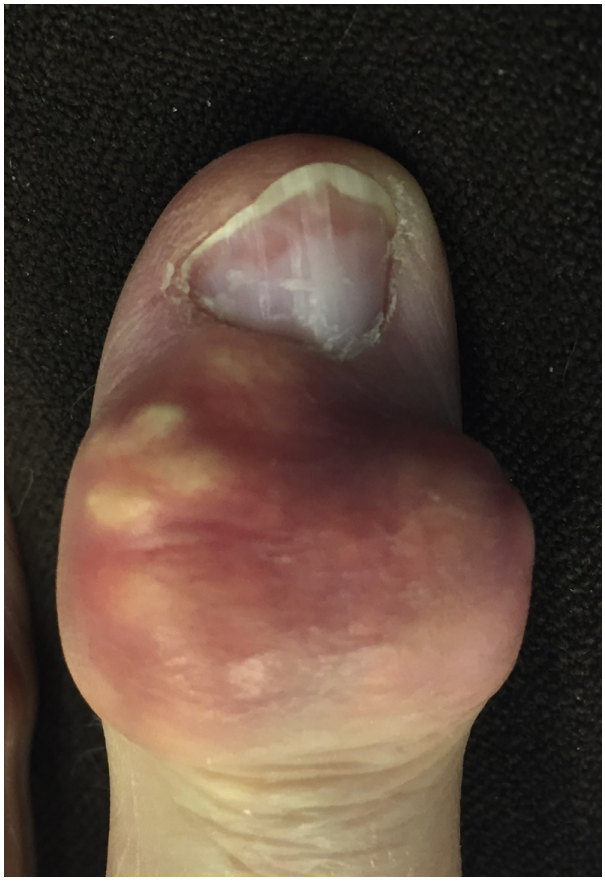

Fig. 6. Voluminous tophi.

to matrix compression[20] (**Fig. 6**). When tophi are located at the tip of a toe, friction may lead to a chronic, crusted, nonhealing wound.[81] Besides the classical tophi, gout may manifest as abrupt and acute isolated painful hallux in the early morning. Less frequently, gout tophi could involve finger pad with a sometimes challenging clinical presentation as periungual hyperkeratotic lesion mimicking squamous cell carcinoma.[82] Radiology, although frequently normal, may be useful in chronic stage showing asymmetrical swelling and subcortical cysts without erosion.[83] It is not specific in early or acute gout.[83] Diagnosis is based on a combination of clinical findings, laboratory tests and imaging.[80,83] A demonstration of monosodium urate crystals deposition permits a definitive diagnosis of gout.[83] Interestingly, urate crystals may be found in the nail plate and could be, according some authors, a new noninvasive diagnostic method for gout.[84] Once installed, tophi may last years before resolving or remain forever, even with appropriate medical treatment.[85] Thus, early urea-lowering treatment is mandatory.[86] Surgery may be an option in selected cases, but delayed healing is the rule.[87]

Yellow Nail Syndrome

The yellow nail syndrome is an acquired rare entity affecting middle-age adults of unknown etiology characterized by the triad: yellow nails, chronic respiratory diseases, and lymphedema.[88,89] The 3 symptoms are not always present, but the typical nail alterations are sufficient.[90,91] Nails are the only manifestation in one-third of patients with yellow nail syndrome. Hereditary cases are anecdotal.[92–94] Nail changes are pathognomonic: the nail growth is much decreased or stopped; the nail plate is thick with an opaque yellow–green to brownish discoloration; there is a lack of cuticle with paronychia and a transverse and longitudinal overcurvature leading to onycholysis and sometimes nail shedding[90,92] (**Fig. 7**). This nail was described by Moffitt and de Berker[95] as the nail that grows one-half as fast but twice as thick. Both fingernails and toenails are affected, and usually all the nails involved. The diagnosis of yellow nail syndrome is clinical and anamnesis often

Fig. 7. Pathognomonic nail changes in yellow nail syndrome: thick opaque yellow nail plate with missing cuticle and multiple transversal lines.

unveil some chronic symptoms such as respiratory manifestations (56%–71%) like chronic cough, pleural effusion, chronic obstructive lung disease, chronic bronchitis, recurrent pneumonia, bronchiectasis, and sinusitis.[92,93]

Lymphedema is observed in 29% to 80% of patients with yellow nail syndrome.[92,93] It is a nonpitting edema usually involving symmetrically the lower limbs, but the hands or the face can be involved.[93] Yellow nail syndrome has also been described in association with various diseases, but most of them are anecdotal[92,93] (**Box 10**).[20,90,92,93] Amazingly, nail changes similar to yellow nail syndrome have been exceptionally reported with nail lichen planus.[96] Recently, several reports suggest titanium as a potential cause of yellow nail syndrome.[97] Titanium may be encountered in implants, foods, personal care products, or medications.[97,98] Eviction of titanium sources may allow partial or complete healing, but it remains controversial.[97,98] Spontaneous improvement of the nails has been reported in 10% to 30% of cases.[90,94] Improvement or even resolution of the nail disease has been described with the treatment of the respiratory or lymphedema manifestations of the yellow nail syndrome.[90,92] There is no therapeutic consensus for yellow nail syndrome. High-dose vitamin E (1000–1200 IU/d) has been effective in some case studies.[90,92] Its association with systemic antifungals (itraconazole [400 mg/d a wk/mo] or fluconazole [300 mg/wk]) for at least 6 months, can be beneficial for their stimulating nail growth effect[92,99]

Box 10
Systemic diseases associated with yellow nail syndrome

Neoplasia

- Lung cancer
- Larynx carcinoma
- Breast carcinoma
- Hodgkin lymphoma
- Multiple myeloma
- Melanoma
- Mycosis fongoides
- Renal cell carcinoma
- Endometrial adenocarcinoma
- Gallbladder adenocarcinoma

Immunodeficiency states

Infectious disease

- Tuberculosis
- Syphilis

Autoimmune disease

- Rheumatoid arthritis
- Systemic lupus erythematosus
- Guillain-Barré syndrome
- Raynaud phenomenon

Endocrine disorders

- Diabetes mellitus
- Thyroid disease

Myocardial infarction

Nephrotic syndrome

Data from Refs.[20,90,92,93]

Connective Tissue Diseases

Many nonspecific nail alterations can be observed in autoimmune diseases and only few of them are suggestive for a specific disease (**Table 1**). Nevertheless, nail abnormalities are frequent and can be the initial sign of these diseases.[100] The most affected part is the proximal nail fold, especially on fingernails.[100] Periungual erythema, telangiectasia, and hemorrhages are observed commonly.[100,101] These nail signs should alert the clinicians and nailfold capillaroscopy is mandatory for differential diagnosis (see below nail fold capillary).

In SSc, fingernails changes are present in up to 80% and seem to be associated with more severe diseases.[101] Raynaud phenomenon is one of the earlier symptoms of SSc. Proximal nailfold erythema, telangiectasias and hemorrhages are frequent.[20,101,102] Chronic paronychia and a

Table 1
Suggestive nail abnormalities in connective tissue diseases

	Suggestive Nail Abnormalities
SSc	Parrot beak nails Pterygium inversum unguis
SLE	Onycholysis Pterygium inversum unguis
DE	Hypertrophic cuticles (Manicure's sign) and cuticular hemorrhages Gottron's papules
AR	Bywaters lesions

Data from Refs.[20,100,101,114]

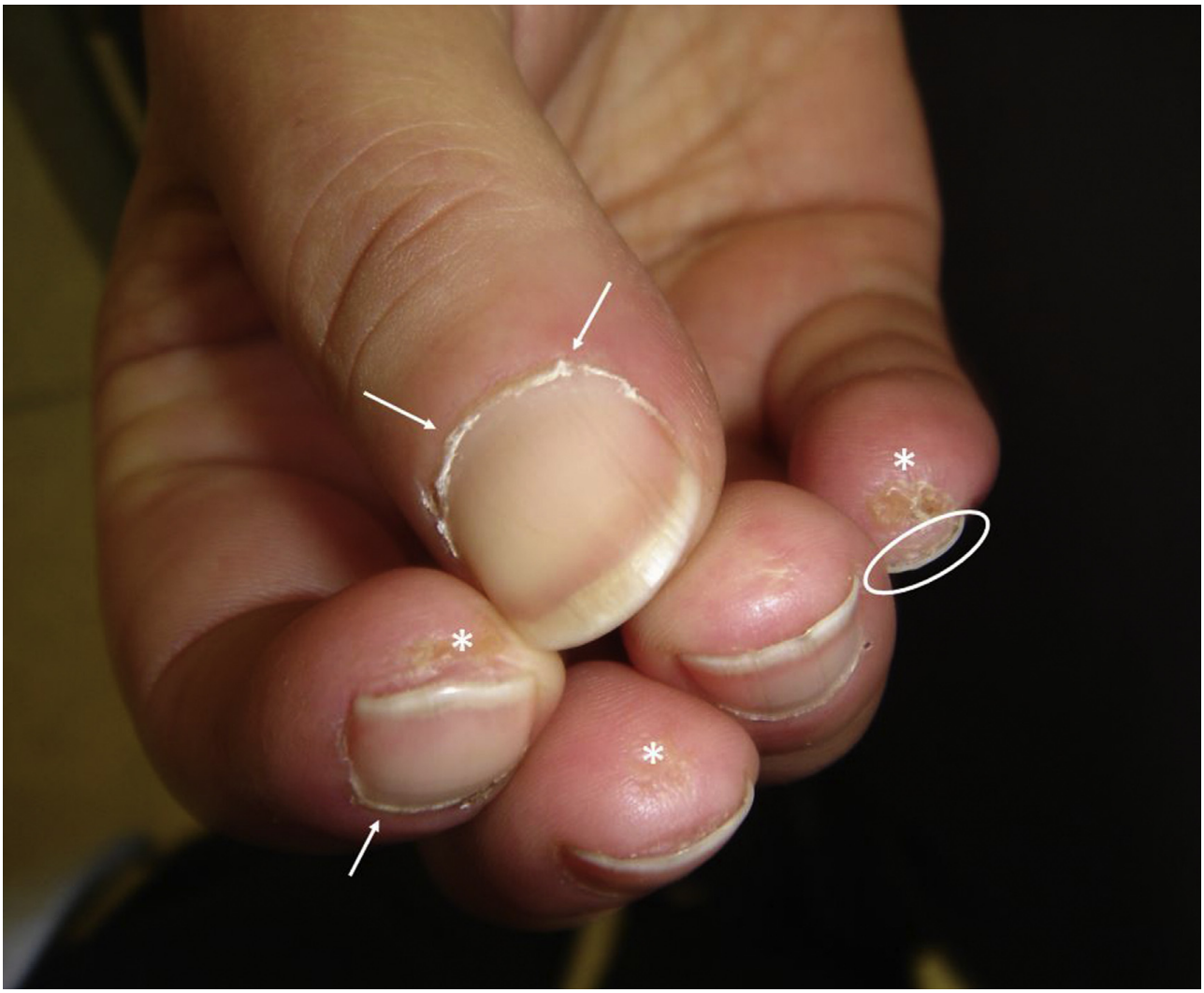

Fig. 8. Digital ulcerations (*white asterisk*), pterygium inversum unguis (*white ring*), and thickened cuticules (*white arrows*) in patient with systemic sclerosis.

thickening and enlarged cuticle can be seen[20,101,102] (**Fig. 8**). Other features reported are absent or red lunula, a white dull color of the plate, splinter hemorrhages, nail plate thinning and ridging, trachyonychia, and transverse overcurvature of the nail plate.[20,100–102] The latter is associated with disease activity.[100] In the most severe cases, destruction of the terminal phalanges leads to brachyonychia or even anonychia.[20] Two specific nail changes can be observed in SSc, namely, parrot beak nail and pterygium inversum unguis[20] (see **Fig. 8**). Parrot beak nails is the bending of the nail plate around the fingertip resulting from soft tissue atrophy in severe acrosclerosis[20] (discussed elsewhere in this article). Sclerodactyly—a localized skin thickening of the extremities in advanced cases—is observed in up to 90% of these patients.[20] Ischemic changes of the fingertip with ulcerations are common (see **Fig. 8**) and digital gangrene can occur.[20,101]

In systemic lupus erythematosus (SLE), a wide range of nail abnormalities may be observed in 25% to 55% of patients.[103,104] None of them are sufficiently distinctive to allow a definitive diagnosis.[103,105,106] Erythema and telangiectasia of the proximal nailfold (**Fig. 9**), splinter hemorrhages, thinning of the plate, longitudinal ridging, melanonychia, ventral pterygium, and red lunula are frequently described.[100,106] Many other nail changes have been reported in systemic lupus erythematosus, including Beau's lines, onychomadesis, pitting, chronic paronychia, subungual hyperkeratosis, leukonychia, increased transverse or longitudinal nail curvature, pincer nails, and clubbing.[20,105,107] Onycholysis seems to be the most common finding (25%–40%).[103,104] Red lunula can be the presenting sign of systemic lupus erythematosus[73] and has been found in up to 20% of patients with lupus.[74] Longitudinal melanonychia or diffuse blue–black chromonychia can occur in systemic lupus erythematosus, especially in patients with darker skin.[20,108] These pigmentations could result from the direct involvement of the nail matrix by lupus or be drugs related (antimalarial agents).[108] Different studies reported an

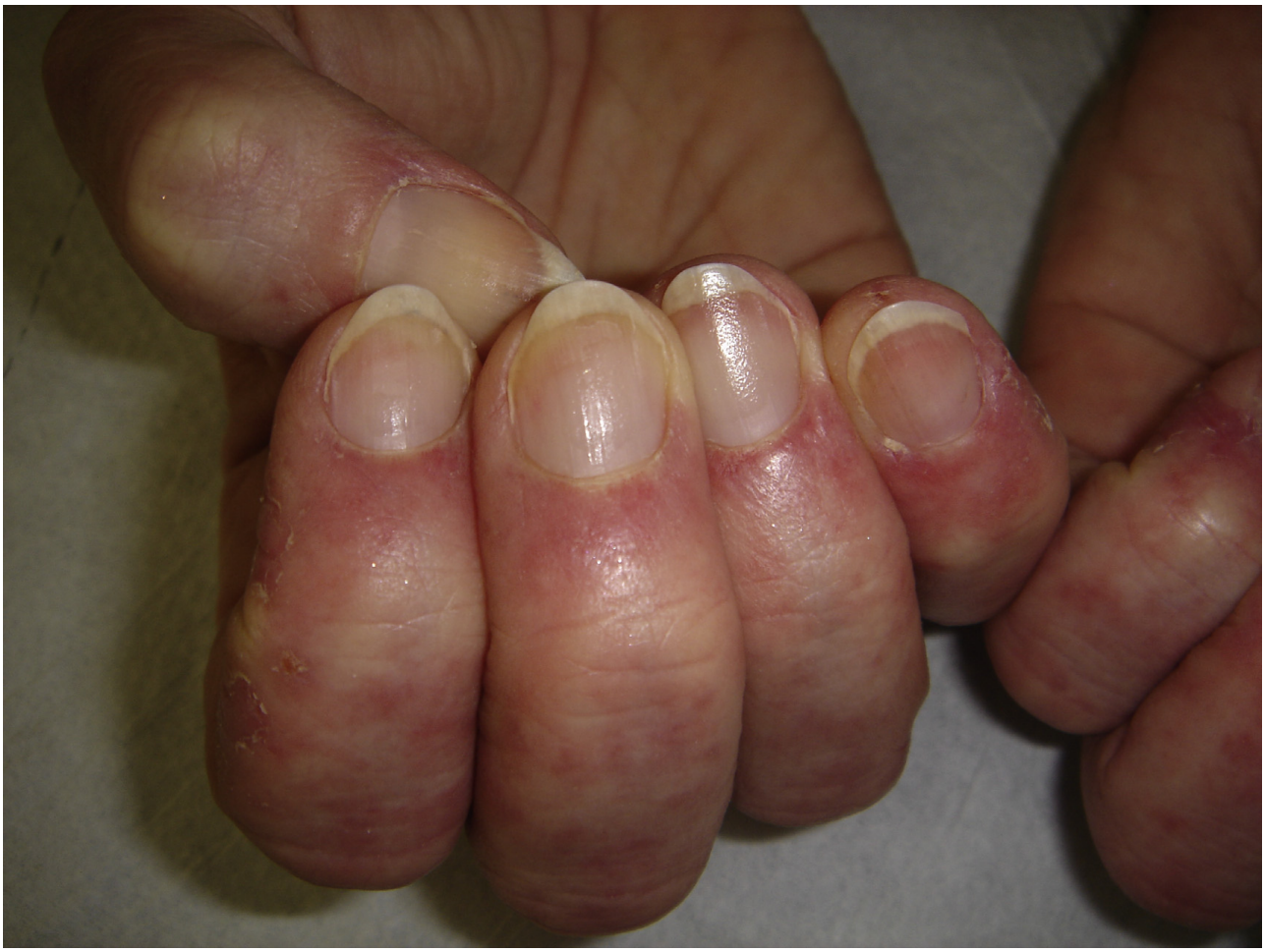

Fig. 9. Periungual erythema in systemic lupus erythematosus.

association between splinter hemorrhages[100] or nailfold erythema and onycholysis[106] with disease activity. Overall, patients with systemic lupus erythematosus with nail abnormalities have a higher damage organ index, disease activity, and nailfold capillaroscopy abnormalities, suggesting that nail involvement might be related to chronic microvascular damages.[104,105] In discoid lupus erythematosus, nail involvement is unusual and never restricted to the nail unit.[103] Severe subungual hyperkeratosis, longitudinal ridging, and nail atrophy can occur with sometimes the typical discoid lupus erythematosus lesions on the perionychium (**Fig. 10**).[103] Patients with discoid lupus erythematosus with nail changes are at a higher risk to develop systemic lupus erythematosus.[109]

In dermatomyositis (DM), hyperkeratotic and thickened cuticles are common with frequent nailfold erythema and telangiectasia associated (**Fig. 11**). This condition may be painful and is called the manicure's sign. It is not pathognomonic and can be observed in SSc and systemic lupus erythematosus. The parallelism between cuticular changes and dermatomyositis activity are controversial.[110] Gottron's papules—violaceous flattened papules on the dorsum of the metacarpophalangeal and interphalangeal joints—can be observed[20] (see **Fig. 11**). Other findings are splinter hemorrhages, red lunula, trachyonychia, pitting, Terry's nail, and pterygium inversum unguis (less frequent than in SSc and systemic lupus erythematosus).[20] Periungual ischemic lesions can occur and might be a predictive sign of malignancy in adult dermatomyositis.[111] Mechanic's hands are nonpruritic hyperkeratotic scaly eruption of the lateral surfaces of the digits with sometimes a fissuring pulpitis, mimicking the hands of a manual labourer.[112,113] It is observed in antisynthetase syndrome, which is associated with diffuse interstitial lung disease, inflammatory myopathy, polyarthritis, and cutaneous signs.[112] Mechanic's hands are also described in patients with dermatomyositis, systemic lupus erythematosus, and SSc.[113]

In patients with rheumatoid arthritis, small punctiform painless hemorrhagic lesions on the nailfold and pulp, named the Bywaters lesions, are specific.[114] These lesions are small infarcts from necrotizing vasculitis.[20,114] Splinter hemorrhages,

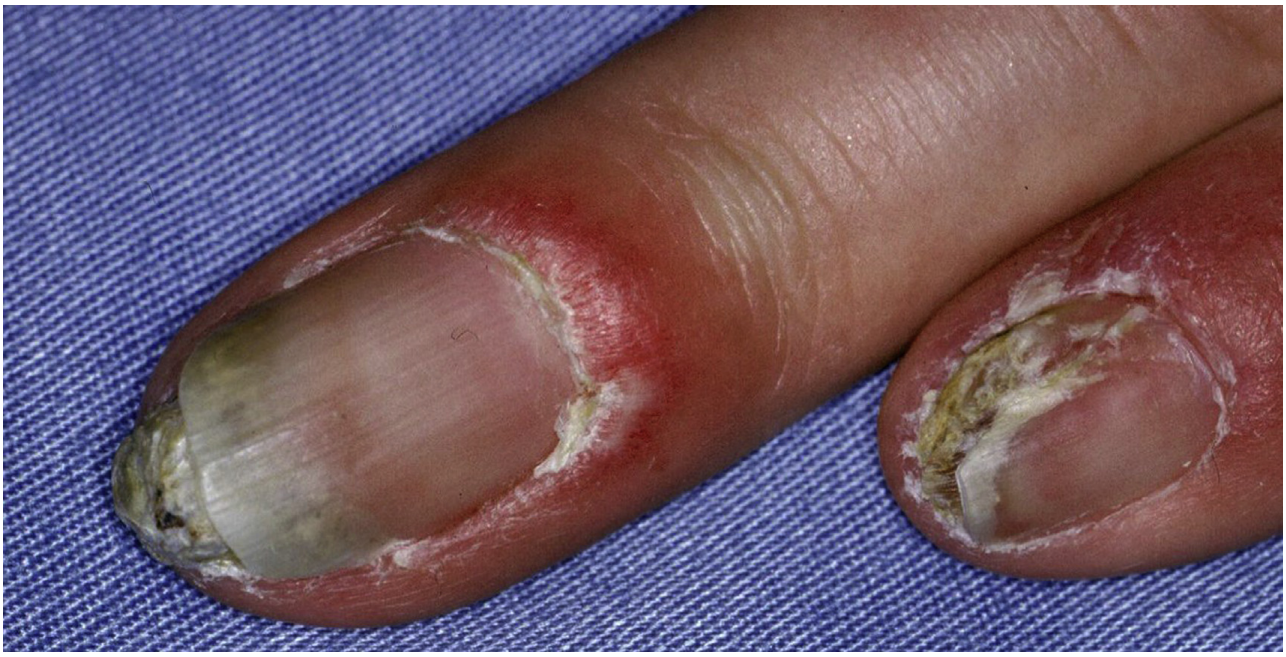

Fig. 10. Erythema and scaling of the perionychium with severe subungual hyperkeratosis in discoid lupus erythematosus.

red lunula (mottled red lunula), longitudinal ridging, onycholysis, and a white dull color of the nail plate are frequent.[20,100] Muehrcke's lines were also reported.[115] Gangrene is rare and observed in severe form of rheumatoid vasculitis.[20] Rheumatoid nodules can be localized in the perionychium.[20] In rheumatoid arthritis, yellow nail syndrome can occur spontaneously or after treatment initiation (D-penicillamine or bucillamine)[116]

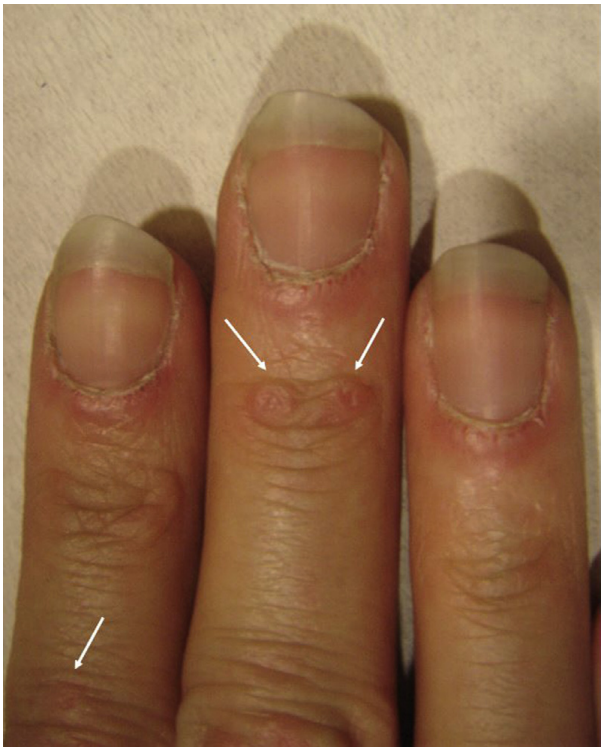

Fig. 11. Manicure's sign and Gottron papules (*white arrows*) in dermatomyositis.

Tuberous Sclerosis Complex

Tuberous sclerosis complex (TSC) is a multisystemic autosomal dominant genetic disorder related to mutation of tumor suppressor genes: TSC1 or TSC2, coding respectively for hamartin and tuberin protein, important regulators of the mechanistic target of rapamycin complex 1 pathway, which controls cell growth and proliferation.[117,118] This syndrome predisposes to hamartoma formation in many organs, especially in central the nervous system, kidneys, lungs, heart, and skin.[117,118] Ungual fibromas are the last skin manifestations of TSC, occurring at puberty and increasing in number with age.[117] Ungual fibromas are usually not present at the time of the initial diagnosis, but multiple ungual fibromas (Koenen tumors) must alert the clinician (**Fig. 12**). They are a major diagnostic criterion of TSC and involve 20% to 80% of patients.[117,119]

Ungual fibromas are pedunculated, flesh-colored benign tumors, with a pointed hyperkeratotic extremity. When located beneath the proximal nail fold, ungual fibromas can rest on a longitudinal groove, which are sometimes the only sign of ungual fibromas.[119]

The majority of ungual fibromas are periungual and located on toenails (especially the fifth), but subungual and fingernails lesions are also seen.[119] Others nail abnormalities have been reported in TSC; longitudinal leukonychia, splinter hemorrhages, onychogryphosis, and cuticular hyperkeratosis.[119] Red comets are a recently described sign that could be specific of TSC. Red comets are partially blanchable reddish

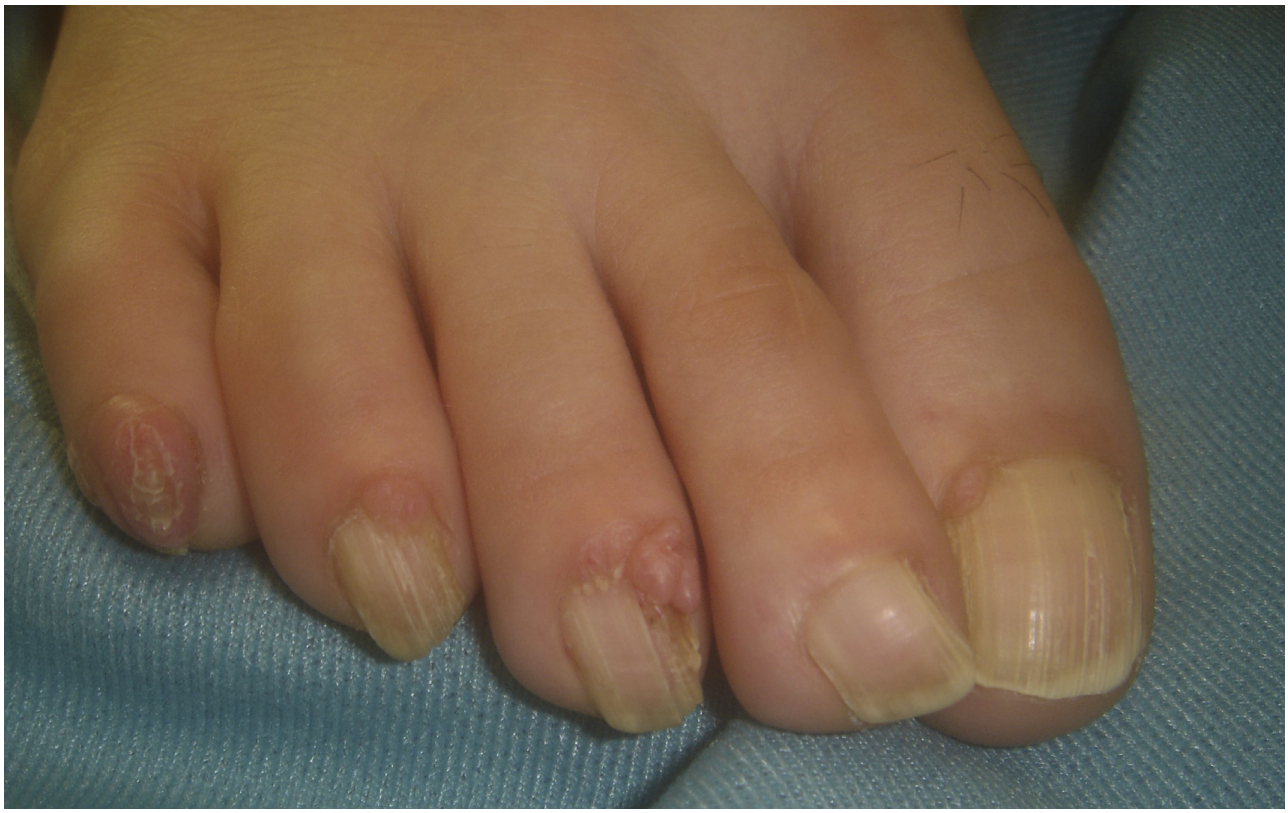

Fig. 12. Multiples ungual fibromas (Koenen tumors) and longitudinal grooves in tuberous sclerosis complex.

longitudinal streaks with a narrow proximal tail and a dilated distal head with sometimes a surrounding whitish halo. They affect fingernails most frequently and could be multiple[119,120]

Acrokeratosis Paraneoplastica of Bazex and Dupré

Acrokeratosis paraneoplastica (AP), also called Bazex syndrome, is a rare but distinctive paraneoplastic dermatosis. It is mostly associated with squamous cell carcinomas of the upper respiratory or digestive tracts but other malignancies have been described.[121–124] It is always associated with malignancy, and in the majority of the cases (63%) cutaneous lesions precede the symptoms with a mean time of 11 months.[124] The pathogenesis remains unclear.[122,124] Acrokeratosis paraneoplastica is typically seen in Caucasian males more than 40 years old.[122,124] Initially, the lesions are ill-defined erythematosquamous plaques symmetrically located on the acral sites: ears, nose, feet, and hands. Parallel to cancer progression, skin lesions evolve to the palms, soles, and cheeks and finally to the arms, legs, scalp, and trunk. Typically, plantar and palmar keratoderma spares the central part of the soles, which can be a clue to the diagnosis.[122–124] Violaceous erythema, erosions, and crusts might be present, and the distribution could be asymmetrical.[122,124] In dark-skinned patients, hyperpigmentation predominates.[123,124] Some cases of vesicular to bullous lesions are reported, particularly on the digits, mimicking autoimmune bullous disorders. Most of the lesions are asymptomatic, but intensive itch and pain are mentioned.[122,124] The nails are almost always involved (75%)[124] and one of the earliest manifestations.[125] The toenails are more severely affected than the fingernails.[125] First, nail plates are thin, brittle, and cracked. Then they become thick with subungual hyperkeratosis, onycholysis and white to yellowish color, mimicking nail psoriasis.[124,125] Longitudinal and transversal lines are seen.[124,125] Onychomadesis, paronychia, and pigmentation may occur.[123,124] Nail changes could be quite variable, ranging from simple thickening to complete nail atrophy.[125] The perionychium is typically covered with erythematosquamous papules.[124,125] Histopathology is often nonspecific.[122,124] Upon suspicion, a complete physical examination and an exhaustive work-up (otolaryngologic examination, chest radiographs, blood tests with complete blood cell count, erythrocyte sedimentation rate, biochemistry profile, tumor markers, and a test for occult blood in stool) should be performed.[122,123] If this first work-up is unrevealing, gastrointestinal endoscopy and colonoscopy and further medical imaging should be done.[122,123] For highly suspicious acrokeratosis paraneoplastica with no malignancy detected, a close follow-up every 3 months seems

appropriate.[123] The classical therapies for inflammatory skin diseases (steroids, retinoids, and phototherapy) are not efficient in these paraneoplastic lesions, except sometimes to control the symptoms.[122] The only effective therapeutic option is the treatment of the underlying neoplasia, leading to a rapid regression of the cutaneous lesions in 90% of patients.[122,124] Unlike the skin, nail changes often remain or show a really slow regression.[122,124] In case of malignancy recurrence, the skin lesions often relapse[122,124]

CLINICS CARE POINTS

- Beau's lines are frequent.
- If multiples Beau's lines, check history for the culprit.
- Splinter hemorrhages are frequent but not specific.
- If occurring in more than one fingernail, a systemic disease has to be ruled out.
- When facing lichenoid alterations perform a biopsy to rule out:
  - Amyloidosis
  - Sarcoidosis
  - Graft-versus-host disease
  - Dyskeratosis congenita
- Clubbing should be differentiated from pseudoclubbing.
- It may arise from many severe systemic diseases especially neoplastic, pulmonary, cardiac and digestive.
- Complete history and physical examination are mandatory. Additional exams will be performed according to symptoms and signs.
- Hypertrophic osteoarthropathy syndrome is often paraneoplastic and need an aggressive screening.
- Terry's nails first exclude hepatic diseases.
- Half and half nails first exclude renal diseases.
- Muehrcke's nails first check albuminemia.
- Nailfold capillaroscopy is a standard non-invasive and reproductive diagnostic tool, assessing microcirculation.
- The main indications for nailfold capillaroscopy are:
- Differentiate primary to secondary Raynaud phenomenon
- Work-up of all connective tissue disorders
- Systemic sclerosis diagnosis and prognosis
- In systemic disorders, longitudinal melanonychia are multiples.
- In case of multiples acquired pterygium inversum unguis, rule out autoimmune disease, especially systemic sclerosis and systemic lupus erythematosus.
- Slowed or no nail growth.
- Yellow to green to brown discoloration.
- Chronic or subacute proximal nail fold inflammation and disappearance of cuticle.
- Thick, hard and opaque nail plate.
- Patients with yellow nail syndrome:
  - Ask about sinusal/pulmonary symptoms.
  - Perform chest imaging.
  - Involve ENT and pneumologist.
  - Treat underlying disease aggressively.
  - Vitamin E and fluconazole are first line treatment.
  - Keep titanium in mind.
- In connective tissue diseases, nail changes are frequent and mainly non specific but can be the presenting sign.
- Fingernails and proximal nailfold are mostly affected.
- Some nail abnormalities are associated with disease activity.
- Nails should always be evaluated in autoimmune diseases.
- If more than one periungual fibrokeratoma rule out tuberous sclerosis complex.
- Acrokeratosis paraneoplastica is always paraneoplastic and mostly associated with squamous cell carcinomas of the upper respiratory or digestive tracts.
- Nails are almost always involved and one of the earliest manifestations.
- If acrokeratosis paraneoplastica is suspected, a detailed patient history, a complete physical examination and an exhaustive diagnostic work-up needs to be performed.

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DISCLOSURE

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