# 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.

M. Holzberg (✉)
Emory University School of Medicine, Department of Dermatology, Atlanta, GA, USA
e-mail: mark@theholzbergs.com



R. L. Baran (ed.), *Advances in Nail Disease and Management*, Updates in Clinical Dermatology,
https://doi.org/10.1007/978-3-030-59997-3_9

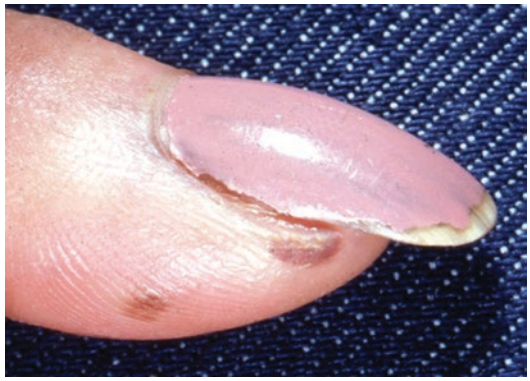

**Fig. 9.1** Bywaters lesions

## 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

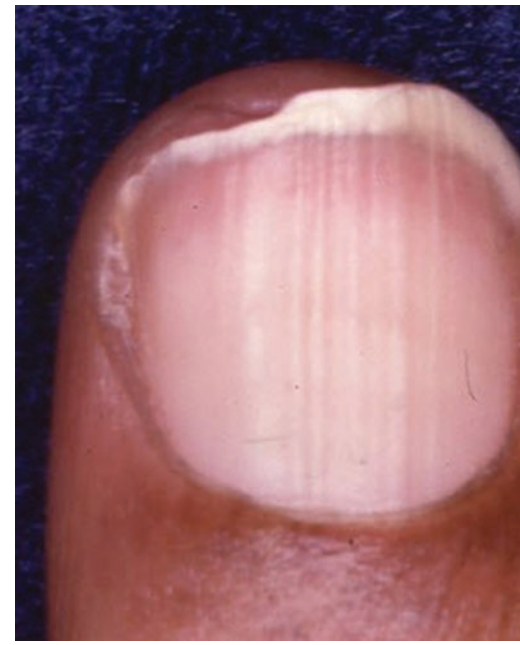

**Fig. 9.2** Terry's nail

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].

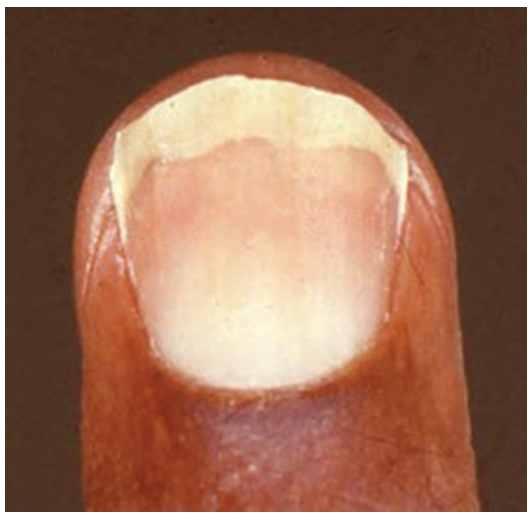

**Fig. 9.3** Half-and-half nail

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

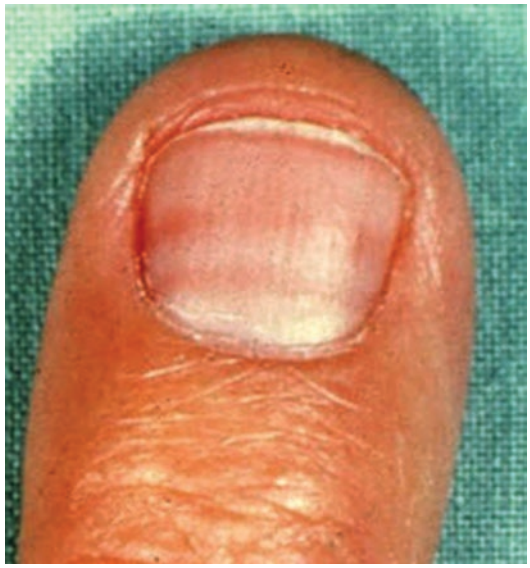

**Fig. 9.4** Muehrcke's lines

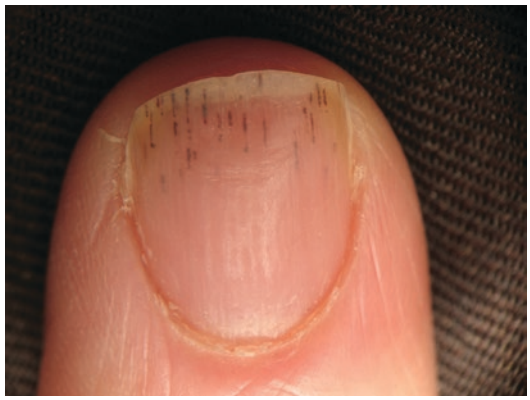

**Fig. 9.5** Splinter hemorrhages

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.

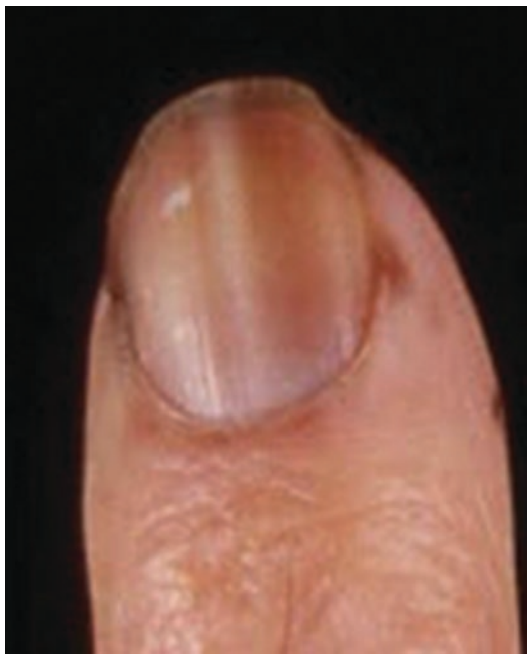

**Fig. 9.6** Peutz-Jeghers syndrome

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-

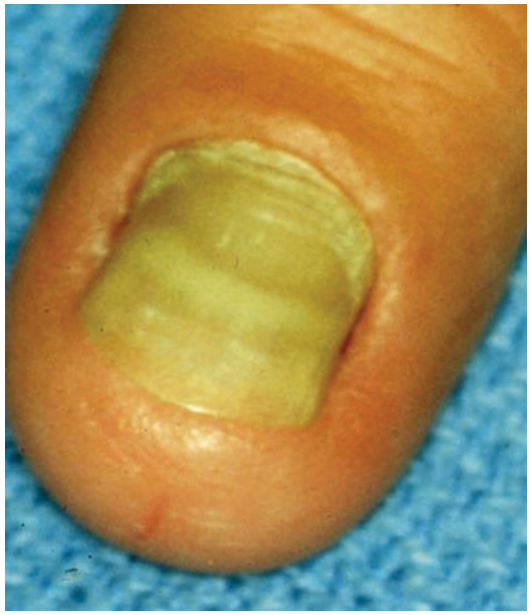

**Fig. 9.7** Yellow nail syndrome

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

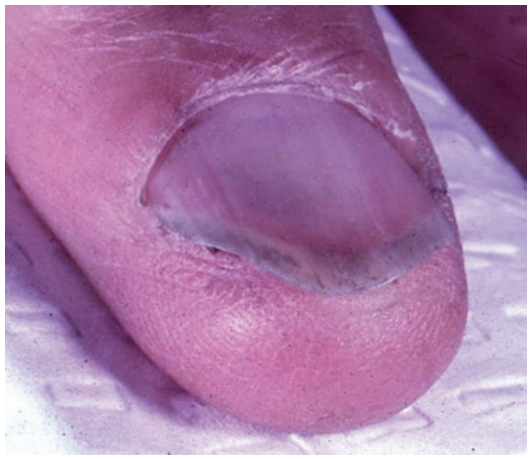

**Fig. 9.9** Koilonychia

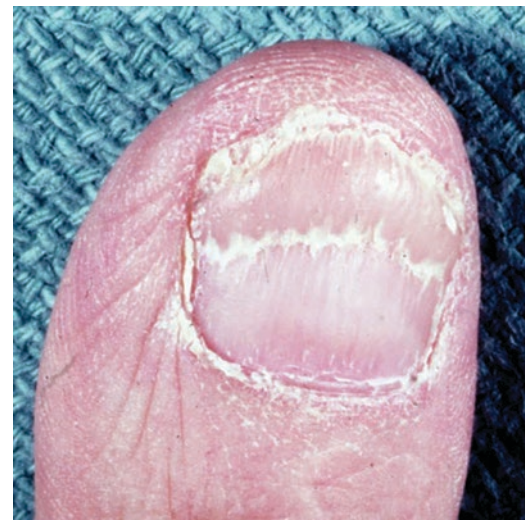

**Fig. 9.10** Beau's line

[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.

## Bibliography


1. Holzberg M. The nail in systemic disease. In: Baran R, editor. Baran & Dawber's disease of the nails and their management. West Sussex: Wiley-Blackwell; 2012. p. 315–412.
2. Herrick AL, Moore TL, Murray AK, et al. Nail-fold capillary abnormalities are associated with anticentromere antibody and severity of digital ischaemia. Rheumatology (Oxford). 2010;49(9):1776–82.
3. Mager JJ, Westermann CJ. Value of capillary microscopy in the diagnosis of hereditary hemorrhagic telangiectasia. Arch Dermatol. 2000;136(6):732–4.
4. Kluger N. Nail fold vasculitis in rheumatoid arthritis (Bywaters lesions). Presse Med. 2017;46(6 Pt 1):625–6.
5. deBerker D. Erythronychia. Dermatol Ther. 2012;25(6):603–11.
6. Morrissey KA, Rubin AI. Histopathology of the red lunula: new histologic features and clinical correlations of a rare type of erythronychia. J Cutan Pathol. 2013;40(11):972–5.
7. Wollina U, Barta U, Uhlemann C, et al. Lupus erythematosus-associated red lunula. J Am Acad Dermatol. 1999;41(3 Pt 1):419–21.
8. Roest YBM, van Middendorp HT, Evers AWM, et al. Nail involvement in alopecia areata: a questionnaire-based survey on clinical signs, impact on quality of life and review of the literature. Acta Derm Venereol. 2018;98(2):212–7.
9. Terry R. White nails in hepatic cirrhosis. Lancet. 1954;263(6815):757–9.
10. Holzberg M, Walker HK. Terry's nails: revised definition and new correlations. Lancet. 1984;1:896–9.
11. Udell JA, Wang CS, Tinmouth J, et al. Does this patient with liver disease have cirrhosis? JAMA. 2012;307(8):832–42.
12. Nelson N, Hayfron K, Diaz A, et al. Terry's nails: clinical correlations in adult outpatients. J Gen Intern Med. 2018;33(7):1018–9.
13. Oanță A, Iliescu V, Tărean S. Half and half nails in a healthy person. Acta Dermatovenerol Croat. 2017;25(4):303–4.
14. Bean W. A discourse on nail growth and unusual fingernails. Trans Am Clin Climatol Assoc. 1963;74:132–67.
15. Lindsay P. The half-and-half nail. Arch Intern Med. 1967;119:583–7.
16. Masmoudi A, Darouiche MH, Sala HB, et al. Cutaneous abnormalities in patients with end stage renal failure on chronic hemodialysis. A study of 458 patients. J Dermatol Case Rep. 2014;8(4):86–94.

17. Dyachenko P, Monselise A, Shustak A, et al. Nail disorders in patients with chronic renal failure and undergoing haemodialysis treatment: a case-control study. J Eur Acad Dermatol Venereol. 2007;21(3):340–4.
18. Zágoni T, Sipos F, Tarján Z, et al. The half-and-half nail: a new sign of Crohn's disease? Report of four cases. Dis Colon Rectum. 2006;49(7):1071–3.
19. Pellegrino M, Taddeucci P, Mei S, et al. Half-and-half nail in a patient with Crohn's disease. J Eur Acad Dermatol Venereol. 2010;24(11):1366–7.
20. Afsar FS, Ozek G, Vergin C. Half-and-half nails in a pediatric patient after chemotherapy. Cutan Ocul Toxicol. 2015;34(4):350–1.
21. Martinez MAR, Gregorio CL, dos Santos VP, et al. Nail disorders in patients with chronic renal failure undergoing hemodialysis. An Bras Dermatol. 2010;85:318–23.
22. Salem A, Al Mokadem S, Attwa E, et al. Nail changes in chronic renal failure patients under haemodialysis. J Eur Acad Dermatol Venereol. 2008;22(11):1326–31.
23. Muehrcke R. The fingernails in chronic hypoalbuminemia. Br Med J. 1956;1:1327–8.
24. Stanifer J, Mehta R, Mettu N, et al. Muehrcke's lines as a diagnostic clue to increased catabolism and a severe systemic disease state. Am J Med Sci. 2011;342(4):331.
25. Haber R, Khoury R, Kechichian E, et al. Splinter hemorrhages of the nails: a systematic review of clinical features and associated conditions. Int J Dermatol. 2016;55(12):1304–10.
26. Silverman ME, Upshaw CB. Extracardiac manifestations of infective endocarditis and their historical descriptions. Am J Cardiol. 2007;100(12):1802–7.
27. Usui S, Dainichi T, Kitoh A, et al. Janeway lesions and splinter hemorrhages in a patient with eosinophilic endomyocarditis. JAMA Dermatol. 2015;151(8):907–8.
28. Alzayer H, Hasan MA. Hypereosinophilic vasculitis: a case report. Medicine (Baltimore). 2019;98(17):e15392.
29. Musher D. Ascent to altitude: a benign cause of splinter hemorrhages. J Travel Med. 2012;19(4):243–54.
30. Rennie D. Splinter hemorrhages at high altitude. JAMA. 1974;228:974.
31. Bitterman R, Oren I, Geffen Y, et al. Prolonged fever and splinter hemorrhages in an immunocompetent traveler with disseminated histoplasmosis. J Travel Med. 2013;20(1):57–9.
32. Gottstein B, Pozio E, Nockler K. Epidemiology, diagnosis, treatment, and control of trichinellosis. Clin Microbiol Rev. 2009;22:127–45.
33. Tunc SE, Ertam I, Pirildar T, et al. Nail changes in connective tissue diseases: do nail changes provide clues for the diagnosis? J Eur Acad Dermatol Venereol. 2007;21(4):497–503.
34. Kriseman YL, Nash JW, Hsu S. Criteria for the diagnosis of antiphospholipid syndrome in patients presenting with dermatologic symptoms. J Am Acad Dermatol. 2007;57(1):112–5.
35. Malan M, Dai Z, Jianbo W, et al. Onycholysis an early indicator of thyroid disease. Pan Afr Med J. 2019;32:31.
36. Zaias N, Escovar SX, Zaiac MN. Finger and toenail onycholysis. J Eur Acad Dermatol Venereol. 2015;29(5):848–53.
37. Singh A, Pilania RK, Thapa B, et al. Onycholysis-an uncommon finding in Kawasaki disease. J Clin Rheumatol. 2019. https://doi.org/10.1097/RHU.0000000000001001. [Epub ahead of print].
38. Abramovici G, Keoprasom N, Winslow CY, et al. Onycholysis and subungual haemorrhages in a patient with hand, foot and mouth disease. Br J Dermatol. 2014;170(3):748–9.
39. Erpolat S, Eser A, Kaygusuz I, et al. Nail alterations during pregnancy: a clinical study. Int J Dermatol. 2016;55(10):1172–5.
40. Zali MR, Nejad MR, Al Dulaimi D, et al. Nail changes: unusual presentation of celiac disease. Am J Gastroenterol. 2011;106(12):2202–4.
41. Lipner SR, Scher RK. Evaluation of nail lines: color and shape hold clues. Cleve Clin J Med. 2016;83(5):385–91.
42. Robert C, Sibaud V, Mateus C, et al. Nail toxicities induced by systemic anticancer treatments. Lancet Oncol. 2015;16(4):e181–9.
43. Berard R, Scuccimarri R, Chedeville G. Leukonychia striata in Kawasaki disease. J Pediatr. 2008;152(6):889.
44. Schwartz R. Arsenic and the skin. Int J Dermatol. 1997;36:241–50.
45. Turner M. Unilateral leukonychia and hair depigmentation in multifocal motor neuropathy. Neurology. 2013;81(20):1800–1.
46. Duman I, Aydemir K, Taskaynatan MA, et al. Unusual cases of acquired leukonychia totalis and partialis secondary to reflex sympathetic dystrophy. J Eur Acad Dermatol Venereol. 2007;21(10):1445–6.
47. Hasunuma N, Umebayashi Y, Manabe M. True leukonychia in Crohn disease induced by selenium deficiency. JAMA Dermatol. 2014;150(7):779–80.
48. Cousins E, Cintolesi V, Vass L, et al. A case-control study of the lymphatic phenotype of yellow nail syndrome. Lymphat Res Biol. 2018;16(4):340–6.
49. Gupta S, Samra D, Yel L, et al. T and B cell deficiency associated with yellow nail syndrome. Scand J Immunol. 2012;75(3):329–35.
50. Sarmast H, Takriti A. Yellow nail syndrome resulting from cardiac mitral valve replacement. J Cardiothorac Surg. 2019;14(1):72.
51. Ataya A, Kline KP, Cope J, et al. Titanium exposure and yellow nail syndrome. Respir Med Case Rep. 2015;16:146–7.
52. Hsu TY, Lin CC, Lee MD, et al. Titanium dioxide in toothpaste causing yellow nail syndrome. Pediatrics. 2017;139(1):pii: e20160546. https://doi.org/10.1542/peds.2016-0546.
53. Suzuki T, Tokuda Y, Kobayashi H. The development of yellow nail syndrome after the implantation of a permanent cardiac pacemaker. Intern Med. 2017;56(19):2667–9.

54. Berglund F, Carlmark B. Titanium, sinusitis, and the yellow nail syndrome. Biol Trace Elem Res. 2011;143(1):1–7.
55. Subramanya SH, Hamal D, Nayak N, et al. Onychomycosis due to Candida parapsilosis in a child with ventricular septal defect. An unusual predisposition. Case Rep Pediatr. 2016;2016:7026068.
56. Cecchini M, Doumit J, Kanigsberg N. Atypical presentation of congenital yellow nail syndrome in a 2-year-old female. J Cutan Med Surg. 2013;17(1):66–8.
57. Frankel D, Zaias N. Hereditary yellow nail without a syndrome. Skinmed. 2019;17(1):73–4.
58. Piraccini BM, Urciuoli B, Starace M, et al. Yellow nail syndrome: clinical experience in a series of 21 patients. J Dtsch Dermatol Ges. 2014;12(2):131–7.
59. Baran R, Thomas L. Combination of fluconazole and alpha-tocopherol in the treatment of yellow nail syndrome. J Drugs Dermatol. 2009;8(3):276–8.
60. Matsubayashi S, Suzuki M, Suzuki T, et al. Effectiveness of clarithromycin in patients with yellow nail syndrome. BMC Pulm Med. 2018;18(1):138.
61. Lo Conte C, Allegrini C, Matucci A, et al. Immunoglobulin replacement therapy for yellow nail syndrome. Scand J Immunol. 2018;87(3):e12639. https://doi.org/10.1111/sji.12639.
62. Nakamura J, Halliday NA, Fukuba E, et al. The microanatomic basis of finger clubbing - a high-resolution magnetic resonance imaging study. J Rheumatol. 2014;41(3):523–7.
63. Krishna MR, Sennaiyan UN. Differential clubbing of the lower extremities. J Pediatr. 2016;175:234.
64. Sabnis GR, Phadke MS, Lanjewar CP, et al. Differential cyanosis and clubbing sparing a single limb. J Am Coll Cardiol. 2014;63(14):e33.
65. Manuel DA, Ghosh GC, Alex AG. Atrial septal defect with right-to-left shunt in the absence of pulmonary hypertension. Cardiol Young. 2017;27(3):575–6.
66. Goyal LK, Banerjee S, Yadav RN, et al. Atrial septal aneurysm presenting as clubbing without clinically apparent cyanosis. J Assoc Physicians India. 2015;63(9):75–6.
67. Gallego-Flores A, Carrasco-Cubero C, Aznar-Sanchez JJ, et al. Ankle arthritis and nail clubbing as a form of presentation of Listeria monocytogenes endocarditis. Reumatol Clin. 2016;12(3):178–9.
68. Ozdemir B, Senturk T, Kaderli AA, et al. Postoperative regression of clubbing at an unexpected rate in a patient with aortic and mitral valve replacement due to infective endocarditis. Ir J Med Sci. 2009;178(3):351–3.
69. Iyengar JN, Reddy BKKR. Pulmonary alveolar proteinosis in children: an unusual presentation with significant clinical impact. Indian J Pathol Microbiol. 2018;61(3):418–20.
70. Shiraishi K, Jinta T, Nishimura N, et al. Digital clubbing is associated with higher serum KL-6 levels and lower pulmonary function in patients with interstitial lung disease. Can Respir J. 2018;2018:3640967.
71. van Manen MJG, Vermeer LC, Moor CC, et al. Clubbing in patients with fibrotic interstitial lung diseases. Respir Med. 2017;132:226–31.
72. Tas F, Ertuck K. Digital clubbing as a first clinical presentation of pulmonary metastases in cutaneous melanoma. Postgrad Med. 2018;130(2):278–9.
73. Kraus CN, Sodha P, Vaidyanathan P, et al. Thyroid dermopathy and acropachy in pediatric patients. Pediatr Dermatol. 2018;35(6):e371–4.
74. Narendra BS, Dharmalingam M, Kalra P. Acromegaloidism associated with pituitary incidentaloma. J Assoc Physicians India. 2015;63(6):79–82.
75. Shiji PV, Narayanan S, Niyaz KC, et al. Polycythemia rubra vera presenting as unilateral clubbing due to left subclavian artery thrombosis. J Assoc Physicians India. 2018;66(5):90–1.
76. Murosaki T, Mori K, Nagashima T, et al. Hypertrophic osteoarthropathy associated with esophageal cancer. Intern Med. 2015;54(3):357–8.
77. Horacio MC, Maria VG, Alonso GL. Hypertrophic osteoarthropathy as a complication of pulmonary tuberculosis. Reumatol Clin. 2015;11(4):255–7.
78. Meyer HJ, Leifels L, Bach AG, et al. Secondary hypertrophic osteoarthropathy caused by nonpleural or pulmonary tumors. Medicine (Baltimore). 2017;96(36):e7985.
79. Boyer-Duck E, Dajer-Fadel WL, Hernandez-Arenas LA, et al. Pierre-Marie-Bamberger syndrome and solitary fibrous tumor: a rare association. Asian Cardiovasc Thorac Ann. 2018;26(2):154–7.
80. Ciment AJ, Ciment L. Regression of clubbing after treatment of lung cancer. N Engl J Med. 2016;375(12):1171.
81. Caterson H, Liu K. Hepatobiliary and pancreatic: rare hepatic vascular tumor presenting with hypertrophic osteoarthropathy. J Gastroenterol Hepatol. 2018;33(8):1434.
82. Yamamoto Y, Sasaki Y, Kougame M, et al. Giant oesophageal gastrointestinal stromal tumour presenting with dyspnoea and clubbed fingers. BMJ Case Rep. 2017. https://doi.org/10.1136/bcr-2017-220540.
83. Rhee SM, Park K, Ha YC. Hypertrophic osteoarthropathy in patient with Crohn's disease: a case report. J Bone Metab. 2014;21(2):151–4.
84. Stone O. Spoon nails and clubbing: significance and mechanisms. Cutis. 1975;16:235–41.
85. Walker J, Baran R, Velez N, et al. Koilonychia: an update on pathophysiology, differential diagnosis and clinical relevance. J Eur Acad Dermatol Venereol. 2016;30(11):1985–91.
86. Tahara T, Shibata T, Okubo M, et al. A case of plummer-vinson syndrome showing rapid improvement of Dysphagia and esophageal web after two weeks of iron therapy. Case Rep Gastroenterol. 2014;8(2):211–5.
87. Sawhney M. Ladakhi koilonychia. Indian J Dermatol Venereol Leprol. 2003;69(2):79–80.

88. Park J, Li K. Images in clinical medicine. Multiple Beau's lines. N Engl J Med. 2010;362(20):e63.
89. Gönül M, Cakmak SK, Yayla D, et al. Unilateral Beau's lines in a case of complex regional pain syndrome (reflex sympathetic dystrophy). Indian J Dermatol Venereol Leprol. 2012;78(6):775.
90. Chiu HH, Liu MT, Chng WH, et al. The mechanism of onychomadesis (nail shedding) and Beau's lines following hand-foot-mouth disease. Viruses. 2019: pii: E522. https://doi.org/10.3390/v11060522.
91. El-Domyati M, Abdel-Wahab H, Abdel-Azim E. Nail changes and disorders in elderly Egyptians. J Cosmet Dermatol. 2014;13(4):269–76.
92. van Lümig PPM, Pasch MC. Nail sarcoidosis presenting with longitudinal Erythronychia. Skin Appendage Disord. 2018;4(3):156–9.