Autoimmune disorders: nail signs and therapeutic approaches

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ABSTRACT: Systemic sclerosis (scleroderma, SSc) is an autoimmune disease that targets small and medium-sized arteries and arterioles in the involved tissues, resulting in a fibrotic vasculopathy and tissue fibrosis. Several prominent nail and periungual changes are apparent in scleroderma. Examination of the nail fold capillaries can reveal the nature and extent of microvascular pathology in patients with collagen vascular disease and Raynaud's phenomenon. Among the complications stemming from Raynaud's phenomenon can be painful ischemic digital ulcers. This can be managed, and potentially prevented, through pharmacologic and nonpharmacologic means. Whereas oral calcium channel blockers remain the most convenient therapy, oral endothelin receptor antagonists and intravenous prostaglandins may be important therapeutic advances for ischemic digital vascular lesions.

KEYWORDS: digital ulcers, nail fold capillaroscopy, Raynaud's phenomenon, scleroderma

Introduction

Systemic sclerosis (scleroderma, SSc) is an autoimmune disease that targets small and medium-sized arteries and arterioles in the involved tissues, resulting in a fibrotic vasculopathy and tissue fibrosis. As a consequence, there are several nail and periungual changes that are notable in patients with scleroderma.

Nail changes in scleroderma

Compromise to blood flow with associated Raynaud's phenomenon (vasospasm) can present

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with dramatic reversible pallor (FIG. 1) or cyanosis (FIG. 2). The nails in the scleroderma can also reflect critical digital ischemia. The distal nail bed can appear hyperemic as a result of ischemia of

FIG. 1. Scleroderma: pallor in Raynaud's phenomenon.

FIG. 2. **Scleroderma: cyanosis in Raynaud's phenomenon.**

FIG. 4. **Scleroderma: cyanosis from digital ischemia.**

FIG. 3. **Scleroderma: distal nail bed hyperemia from digital ischemia, splinter hemorrhages, blanching of the proximal nail fold.**

FIG. 5. **Scleroderma: beaking of the nails.**

the distal phalange (FIG. 3) or can be deeply cyanotic without evidence of nutritional blood flow (FIG. 4). Prolonged tissue ischemia with subsequent fibrosis of the nail matrix can also lead to pseudo-clubbing or "beaking" of the nails (FIGS. 5 and 6). Beaking refers to increased longitudinal over-curvature the nail plate, as well as loss of substance of the nail plate and of the hyponychium.

Pitting of the nail plate can occur following inflammation in the nail matrix (FIG. 7). Beading of the nail plate may also be seen (FIG. 8). These teardrop-shaped indentations in the nail plate are caused by tissue ischemia or inflammation, leading to an erratic growth rate from the proximal matrix. This same beading can also occur in rheumatoid arthritis.

Splinter hemorrhages can be present as well (FIGS. 3 and 9). Those in the distal nail bed usually

FIG. 6. **Scleroderma: beaking of the nails.**

FIG. 8. **Scleroderma: beading of the nail plate.**

FIG. 7. **Scleroderma: pitting of the nail plate, keratotic ulcer.**

FIG. 9. **Scleroderma: splinter hemorrhages, hemorrhage into the cuticle.**

result from trauma, but more proximal hemorrhages are pathologic of vascular injury.

In addition to ischemic changes, the nails can certainly show evidence of more common conditions, such as onychomycosis (FIG. 10).

FIG. 10. Scleroderma: onychomycosis.

FIG. 11. Normal nail fold capillaries.

Nail fold capillary changes in scleroderma

Nail fold capillaries provide a readily available window to view the microvascular pathology of collagen vascular disease. Nail fold capillaroscopy is the oldest and arguably the best technique for investigating microvascular involvement in rheumatic disease. Capillaroscopy has its origins in 19th-century Italy, where physician Giovanni Rasori noted that inflamed conjunctivae had "abnormally reddish" coloration associated with "an inextricable knot of capillary loops" (1). In 1911, Lombard was the first to describe applying immersion oil to the periunguium and using a microscope to look at periungual capillaries (2). To this day, nail fold capillaroscopy is performed by placing a drop of immersion oil on the proximal nail fold and then looking at the region through magnification using a dermatoscope or ophthalmoscope. The dermatoscope is the preferable capillaroscopic instrument as it has a larger field of view than that of an ophthalmoscope (2). Nail fold videocapillaroscopy can also be performed as a means of evaluating and retaining images of nail fold capillaries (3).

In a normal nail fold, the capillaries are evenly spaced, evenly sized, and evenly dense (FIG. 11).

There is no one standard of how to grade the severity of capillary derangement in scleroderma. Overall, the earliest signs of scleroderma microangiopathy are enlarged or giant capillaries along with hemorrhages. With progression into the fibrotic phase of the disease, skip areas of avascularity (FIG. 12), capillary enlargement (FIG. 13),

FIG. 12. Scleroderma: skip areas in nail fold capillaries.

and architectural disorganization become more prevalent (FIGS. 14 and 15).

By recent classifications proposed by Cutolo, the pattern of scleroderma microangiopathy ("SSc pattern") can be graded into three subtypes that reflect the stage of the vascular disease: early, active, and late. The early SSc pattern demonstrates few enlarged or giant capillaries, and few capillary hemorrhages, but no evident capillary loss. The active SSc pattern is notable for giant capillaries, capillary hemorrhages, and moderate capillary loss with mild disorganization of the capillary architecture. The late SSc pattern shows severe loss of capillaries with extensive areas of avascularization and disorganization of the capillary array into ramified or bushy capillaries (3).

FIG. 13. Scleroderma: nail fold capillary enlargement.

FIG. 14. Scleroderma: architectural disorganization in nail fold capillaries.

FIG. 15. Scleroderma: architectural disorganization in nail fold capillaries.

In a recent European study of nail fold capillaroscopic examination, 14 of 16 patients with diffuse cutaneous scleroderma had SSc pattern (4). Conversely, in a similar study that also included unaffected controls, none of the 107 controls had SSc pattern on capillaroscopic exam (2).

Dermatomyositis patients' nail fold capillaries have a similar pattern to those in scleroderma, so much so that Maricq classically grouped them into the scleroderma spectrum (SD) pattern (5). This pattern can be seen in scleroderma, mixed connective tissue disease, early undifferentiated connective tissue disorder, dermatomyositis, and overlap syndrome. The key features of this pattern were established as enlarged capillaries (as measured by the caliber of the arterial, apical, and venous dimensions) and areas of avascularity.

Using this SD pattern criteria set forth by Maricq, a recent dermatoscopic study of nail fold capillaries showed SD pattern in 19 of 27 scleroderma patients and 7 out of 11 dermatomyositis patients (6).

Problems with each of the classification systems for the nailfold capillaries are quantifiability and reproducibility. Aiming to address this issue, Herrick and others proposed a system of following capillary dimensions (apex, arterial, venous, and total width), as well as density in loops/millimeter, using video capillaroscopy (7). By this system, the same set of capillaries could be identified and followed longitudinally. Data collected on 11 scleroderma patients versus healthy controls and patients with primary Raynaud's phenomenon demonstrated with statistical significance fewer capillary loops/mm, and an increase in all four capillary dimensions.

A classic study on nail fold capillaroscopy as a means of differentiating primary and secondary Raynaud's phenomenon was published in 1986 by Houtman, Kallenberg, and others. Capillary morphology in 50 subjects with primary Raynaud's phenomenon was indistinguishable from that of the 51 healthy controls. Between primary and secondary Raynaud's phenomenon (39 patients), the decrease in capillary loops was the most distinguishing feature (8). These investigators and others suggest that when a patient presents with Raynaud's phenomenon alone, the presence of abnormal capillary morphology can predict the eventual emergence of an active connective tissue disease (e.g., scleroderma).

To examine potential associations between nail fold capillary pathology and systemic collagen vascular disease, a group of Brazilian researchers published a study of 91 patients demonstrating that severity of capillaroscopic alteration (as measured by avascularity scores and numbers of

"megacapillaries") correlated with lung disease activity in scleroderma patients (9). This correlation was particularly apparent in those patients with 5 or fewer years of disease duration. In that group, 14 of the 19 patients with a severe avascular score had ground glass opacities on high-resolution computed tomography (CT) of the chest. None of the eight patients with normal or mild avascular score had CT abnormalities.

Another study examining the link between nail fold microangiopathy and systemic micro-angiopathy looked at 20 patients with primary Raynaud's phenomenon, and 53 patients with secondary Raynaud's phenomenon associated with scleroderma. They measured the patients' carotid and femoral arterial wall mechanics using a duplex scanner and then compared the two groups (10). Although there were no statistically significant differences in intima-media thickness or femoral artery elasticity between the two groups, the scleroderma patients had significantly impaired carotid elasticity compared with the patients with primary Raynaud's. As such, being able to find the SSc pattern of secondary Raynaud's phenomenon by nail fold capillary examination may identify patients at risk for visceral vascular disease with abnormal regional blood flow and dysfunctional vascular reactivity (i.e., coronary artery involvement) (3).

Periungual changes in scleroderma

Apart from nail fold capillary changes, patients with scleroderma can have other prominent periungual changes.

Immediately adjacent to the nail, the cuticle can become markedly ragged (FIG. 16) or hyperkeratotic (FIG. 17). Hemorrhage into the cuticle can also be present (FIG. 18). Blanching of the proximal nail fold can also appear, as a result of digital ischemia (FIG. 3).

Ischemic changes can result in pterygium inversus unguium (11) (FIG. 19). With an inverse pterygium, the distal nail groove is obliterated, and the nail and dermis remain attached (12). This finding is more common in scleroderma than in dermatomyositis. Erythematous plaques around the nail fold can also occur (FIG. 18).

In the periunguium, ischemia can lead to painful keratotic ulcers (FIGS. 7 and 20). These can also progress to necrosis and gangrene (FIGS. 21–24).

Skin changes on the fingers can include petechiae (FIG. 17) as well as psoriasiform lesions (FIG. 18). Leukoderma can also occur, secondary to scleroderma skin changes (FIG. 25).

FIG. 16. Scleroderma: ragged cuticle.

FIG. 17. Scleroderma: hyperkeratotic cuticle, petechiae.

Differential diagnosis of scleroderma nail and periungual pathology

Nail fold capillaroscopy of a patient with systemic lupus erythematosus (lupus) reveals a marked different pattern from that of scleroderma or

FIG. 18. Scleroderma: hemorrhage into the cuticle, erythematous plaques, psoriasiform lesions.

FIG. 19. Scleroderma: pterygium inversus unguium.

FIG. 20. Scleroderma: keratotic ulcer.

FIG. 21. Scleroderma: necrosis and gangrene.

FIG. 22. Scleroderma: necrosis and gangrene.

dermatomyositis. In lupus, there is meandering and glomerularization of capillaries which is distinctive (FIG. 26). Meandering refers to the appearance of capillaries outside the bounds of their normal "picket fence" configuration, and glomerularization refers to the structural change of the individual capillaries that lead them to resemble renal glomeruli.

FIG. 23. Scleroderma: necrosis and gangrene.

FIG. 24. Scleroderma: necrosis and gangrene.

FIG. 25. Scleroderma: leukoderma.

FIG. 26. Systemic lupus erythematosus: glomerularization of nail fold capillaries.

While similar on a capillaroscopic level, around the nail, scleroderma, and dermatomyositis differ markedly. In scleroderma, the skin between the joints is fibrotic (FIG. 27). However, in dermatomyositis, the skin between the joints is spared, with involvement centered over the interphalangeal joints themselves (FIGS. 28 and 29). Erythematous, scaly skin over the interphalangeal joints in der-matomyositis is Gottron's sign. Also, dermatomyositis can yield the signature violaceous Gottron's papule over an interphalangeal joint (FIG. 30). In patients with dermatomyositis or liver disease, Terry's nails may be present, with proximal

FIG. 27. Scleroderma: fibrosis over the phalanges.

FIG. 28. Dermatomyositis: Gottron's sign.

FIG. 29. Dermatomyositis: Gottron's sign.

FIG. 30. Dermatomyositis: Gottron's papule.

blanching of the nail bed (FIG. 31). This can look deceptively similar to distal nail bed hyperemia in scleroderma patients with digital ischemia (FIG. 32). A clue to whether the pallor or the hyperemia is the abnormal part of a nail is to look at the

FIG. 31. Dermatomyositis: Terry's nails.

FIG. 32. Scleroderma: distal nail bed hyperemia.

FIG. 33. Nail fold biopsy.
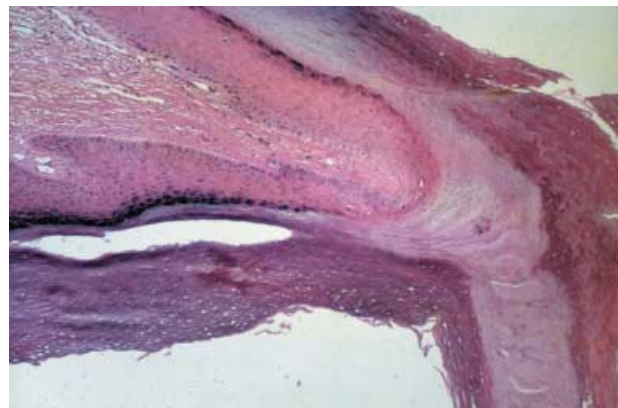
FIG. 34. Haematoxylin and eosin stain of the proximal nail fold.

other nails beds and compare their color to that of the nail in question.

In a patient with primary Raynaud's phenomenon or capillary change without other signs to suggest the diagnosis of a collagen vascular disease, the most expedient way to a diagnosis can be nail fold biopsy (13). After local block with anesthesia, the proximal nail fold can be reflected back from the nail plate and excised in a crescent shape (FIG. 33). The specimen should be bisected, with the half sent for periodic-acid-Schiff (PAS) staining, and half for direct immunofluorescence. An H&E stain of the proximal nail fold demonstrates the location of the cuticle (FIG. 34). With PAS staining, the cuticle in collagen vascular disease is PAS-positive from the protein globules
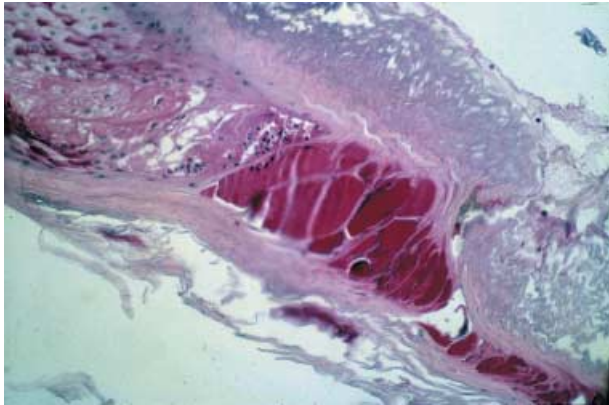
FIG. 35. Periodic-acid-Schiff stain of the cuticle.

that are exuded from leaky capillaries (FIG. 35). DIF patterns of staining can be the earliest diagnostic sign of collagen vascular disease.

Treatment advances

Digital ulcers are a frequent complication of scleroderma, occurring in approximately 50% of scleroderma patients (14). These ulcers are avenues for infection, are very painful, and can cause substantial disability and functional decline. There are several different types of digital lesions that occur in scleroderma, including crusted dry skin with associated fissures, shallow ulcerations secondary to microvascular disease, and deep tissue infarction with gangrene from macrovascular disease (15). Anti-centromere antibody positive patients have recurrent and more severe digital ulcerations with digital amputation (16).

Each type of digital lesion needs to be approached differently. Digital fissures are often mistaken for ischemic lesions but respond best to skin hydration rather than vasodilator therapy. Shallow ulcerations are secondary to microvascular occlusive disease and erode the skin superficially. These lesions are best treated with daily cleansing with soap and water, followed by topical antibiotic ointment (e.g., bacitracin or mupirocin) and coverage with a loose bandage for protection. Deep tissue ischemia and tissue gangrene are a manifestation of both microvascular and larger arterial disease, including disease in the digital arteries, palmar arch, ulnar and radial vessels. These lesions are best prevented by vasodilator and vascular therapy. Debridement of a wound is discouraged unless secondary infection is present, and self amputation of digital infarction is preferred to surgical procedures. Systemic antibiotic therapy is utilized for cellulitis or deep secondary infections, including paronychia.

The pathologic process in scleroderma causes arterial disease in the peripheral circulation. There are two components to the arterial disease: excessive reactivity and vasospasm and a unique vasculopathy characterized by smooth muscle hypertrophy, endothelial cell "injury," and intimal fibrosis (17). The intimal fibrosis is thought to be caused by transformed smooth muscle cells or pericytes that transform to secretory myofibroblasts. This results in luminal narrowing and vascular occlusion. New evidence suggests that Raynaud's phenomenon is in part the result of abnormal function or increased expression of α2c-adrenergic receptors on smooth muscle cells of the cutaneous arteries (18). In scleroderma, there is increased expression of α2c-adrenergic receptors on smooth muscle cells that precedes endothelial cells dysfunction (19). In addition, studies suggest that endothelial cell abnormalities exist that enhance the vasoconstrictive phenotype seen in scleroderma. This occurs as a result of an imbalance in vasoconstrictors (increased release of thromboxane, serotonin, and endothelin) and vasodilators (decreased production of prostacyclin and nitric oxide) known to be released from the endothelial cell to regulate vascular tone (20). Vascular therapy in scleroderma has attempted to reverse these defects via several therapeutic targets.

The most effective therapy for Raynaud's phenomenon is cold avoidance and stress management. Layering warm clothing and maintaining a warm work environment are keys to successful treatment. The standard drug therapy for scleroderma patients with Raynaud's phenomenon is to use a calcium channel blocker. The dihydropyridine class of agents is potent at vasodilatation and is efficacious in the treatment of Raynaud's phenomenon. On average, a moderate reduction of the frequency of attacks and a 35% improvement of severity can be expected according to a recent meta-analysis of scleroderma patients (21). Whereas nifedipine has been studied most extensively, the newer dihydropyridines, including felodipine, amlodipine, and isradipine, appear to be equally effective.

Other commonly used vasodilators are nitrates – either topical, sublingual, or oral – as well as α-sympatholytics, such as prazosin. Although helpful in some patients who cannot tolerate a calcium channel blocker, these agents are of limited value for long-term management of secondary Raynaud's phenomenon.

Several novel therapies are currently being used, and some formal investigations are underway.

These include the use of endothelin inhibitors, phosphodiesterase inhibitors, selective serotonin reuptake inhibitors, angiotensin II receptor inhibitors, and angiotensin-converting enzyme inhibitors.

Recently, the oral endothelin receptor antagonist bosentan has been shown to have beneficial effects in preventing digital ulcers (18). Endothelin is released in response to endothelial injury, and endothelin receptor antagonists exert their effects by blocking endothelin's vasoconstrictive and vascular remodeling actions. In a randomized, prospective, placebo-controlled, double-blind study of 122 patients in 2004, scleroderma patients receiving bosentan had a mean of 1.4 new ulcers during the 16-week treatment period as compared with 2.7 new ulcers for the placebo group. This represented a reduction of 48%. In addition, the patients on bosentan had a statistically significant improvement in hand function during the study (22).

A study soon to be published in *Rheumatology* followed 18 scleroderma patients (12 with limited cutaneous disease, and 6 with diffuse disease) during 6 months of bosentan treatment (23). Using video capillaroscopy, finger systolic pressures, laser Doppler imaging, and questionnaires about hand function, the patients were assessed acutely after receiving bosentan, and then at 4–8-week intervals. This small cohort did not have statistically significant improvement in microvascular structure or function. However, this was an uncontrolled study, and it is possible that bosentan stabilized the patient and prevented what would have otherwise been a worsening of vascular disease and function during the 6 months' time.

A recent trial of sildenafil demonstrated improvement in Raynaud's phenomenon and local blood flow in the capillaries, suggesting that phosphodiesterase inhibitors will be an treatment option in patients who do not respond to a calcium-channel blocker (24).

Selective serotonin reuptake inhibitors are believed to be helpful in the treatment of Raynaud's phenomenon. Fluoxetine (20 mg/day) was compared with nifedipine (40 mg/day) in patients who had primary and secondary Raynaud's phenomenon (25). In this pilot study, fluoxetine improved the frequency and severity of Raynaud's attacks. A positive response was greater in patients who had primary Raynaud's phenomenon versus those who had secondary Raynaud's phenomenon. Although the authors have used each of these novel agents with some success either alone or in combination with the standard calcium channel blocker therapy, their use is generally limited to complex cases not responding to a calcium channel blocker alone.

Activated platelets are the source of several key vasospastic substances – such as serotonin and thromboxane A2 – and could contribute to the vascular disease in scleroderma. Although not fully studied, the present authors recommend that, unless contraindicated, scleroderma patients should be placed on antiplatelet therapy with 81 mg of aspirin daily.

When patients develop larger-vessel digit-threatening ischemia, it is a medical emergency requiring urgent care or hospitalization. A warm environmental temperature, bed rest to decrease trauma and activity of the involved limb, and appropriate pain control are essential. Vasodilator therapy should be maximized with titration of calcium-channel blockers to a full, tolerated dose. Local infiltration of lidocaine or bupivicaine at the base of the involved finger to produce a rapid chemical sympathectomy can improve blood flow and rapidly reduce ischemic pain.

For patients with rapidly advancing ischemic tissue, anticoagulant therapy is initiated; although there are no formal studies, the use of heparin for 24–72 hours during an acute crisis makes sense. Chronic anticoagulation is not recommended unless there is evidence of an underlying hypercoagulable state. In cases of rapidly progressing ischemia that fails to respond to standard vasodilatory therapy, intravenous prostaglandins (e.g., epoprostenol) can be given for several days through a peripheral venous line.

Prostaglandins are being studied for prevention, as well as for treatment, of digital ulcers in scleroderma. A pilot study published in 2006 in the *Journal of the American Academy of Dermatology* placed 12 scleroderma patients on continuous therapy with treprostinil, a prostaglandin analog (26). Each patient had at least one digital ulcer that had not decreased in size in 2 months. Five of the 12 patients dropped out of the study before the 2-week follow up visit because of severe injection site pain, which is a well-documented side effect of treprostinil when administered subcutaneously. Another two subjects withdrew because they required amputation for progressive gangrene in previously ischemic digits. Among the five patients who remained in the study, ulcer size significantly decreased, and no new ulcers occurred. Although that outcome was encouraging, the pronounced injection site pain may limit treprostinil's therapeutic utility.

Proximal or distal (digital) sympathectomy or arterial reconstruction is used for patients

who have failed medical therapy. Digital sympathectomy is the preferred procedure in that it can be coupled with release of the digital artery from extrinsic tissue fibrosis. The long-term outcome is not well documented, and relapse of active vasospasm can recur despite surgical intervention.

All patients who present with a critical ischemic crisis should have a careful assessment to detect any correctable larger vessel disease. Arterial Doppler studies, magnetic resonance angiography, and/or angiography can be used to define the magnitude of larger vessel disease in these selected cases.

To prevent vessel occlusion, antiplatelet drugs have been used. To prevent tissue injury, antioxidants may be beneficial. For vascular remodeling, angiotensin-converting enzyme inhibitors, prostaglandins, statins, and endothelin receptor inhibitors are being investigated (20).

Whether associated with scleroderma, lupus, dermatomyositis, or other collagen vascular diseases, Raynaud's phenomenon can be managed through a combination of the therapies mentioned previously, and through nonpharmacologic means such as avoidance of cold and of medications, which can precipitate worsening of symptoms. Drugs reported to precipitate Raynaud's phenomenon include vasoconstrictive agents – serotonin agonists (i.e., sumatriptan), clonidine, narcotics – and chemotherapeutic agents – bleomycin, cisplatin, vincristine – as well as interferons, estrogens, and cyclosporine. These patients should also be counseled to abstain from the use of nicotine or cocaine (15).

Conclusion

From a practical standpoint, digital vascular disease needs attention and all patients should avoid cold exposure and be considered for vasodilator therapy. The calcium-channel blockers remain the most practical and effective agents to treat Raynaud's phenomenon and potentially to prevent digital ischemic events. Novel therapy for complex cases is now under active investigation.

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