ASK THE EXPERT

# Digital Ulceration in Patients With Scleroderma

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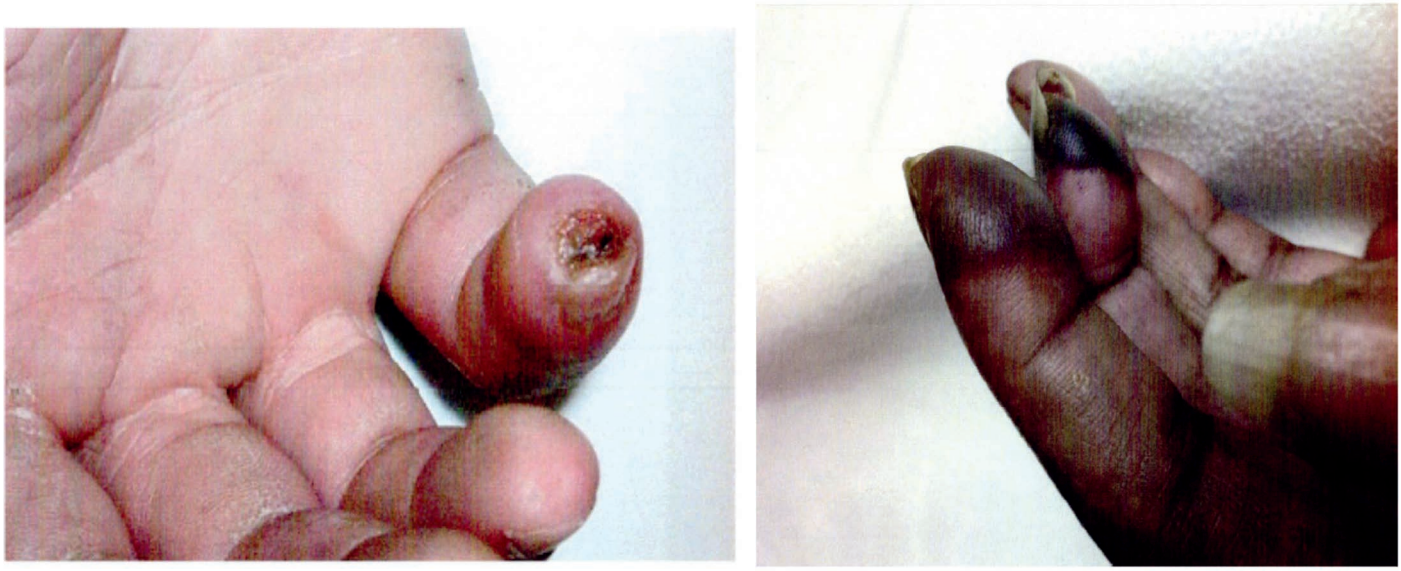
Raynaud's phenomenon (RP) is the most common complication of scleroderma (SSc), affecting over 95% of patients with this disease.[1] Raynaud's phenomenon results from structural and functional abnormalities in the digital arteries and is characterized by intimal proliferation. This proliferation leads to: 1) endothelial damage characterized by upregulation of vasoactive mediators that cause vasoconstriction, and 2) vascular narrowing that further impairs blood flow in these arteries.[2] In addition, increased expression of alpha-2c adrenergic receptors in the digital arteries results in heightened responsiveness to cold-induced adrenergic signals.[3] These factors predispose to vasospasm in the digital arteries, which in turn can lead to tissue ischemia and generation of reactive oxygen species that further propagate local tissue damage. Repeated cycles of damage can lead to ulcerations of the digits with denuded areas of tissue with loss of dermis and epidermis known as digital ulcerations (DU). While less common than RP, DU still occurs in 10% to 54% of SSc patients and represents end-organ damage from vascular disease in SSc.[4] Digital ulceration carries a significant impact, leading to profound disability that impairs psychosocial adjustment to illness and health-related quality of life.[5]

It is imperative to distinguish DU from other lesions on the digits as management differs between causes of ulcerations. Due to the skin involvement in SSc, patients often have dry skin that is prone to fissuring or trauma; in addition, subcutaneous calcinosis can rupture through the skin and cause ulcerations. Osteolysis, loss of bone of the distal phalanx, can also occur in SSc and predispose to non-DU ulcerations. Digital ulcerations are typically found on the volar surface of the fingertip, but can occur around the nailbed on the extensor surface as well (Figure 1).[8] Assessing risk for DU development may be helpful to differentiate from other causes. For example, DU may be more common in men and more prevalent in SSc patients with a history of DU, abnormal nailfold capillaries, and increased erythrocyte sedimentation rate.[6] Other factors associated with development of DU include younger age of onset of SSc, higher severity of skin disease, and presence of interstitial lung disease. There may also be an increased risk of early development of



A B

Figure 1. A) Digital ulcer in a patient with scleroderma. B) Critical ischemia in a patient with scleroderma. Reprinted from Cappelli L, Wigley FM. Management of Raynaud Phenomenon and Digital Ulcers in Scleroderma. *Rheum Dis Clin North Am*. 2015;41(3):419-438, with permission from Elsevier.

DU in patients with antitopoisomerase antibodies.

Management of DU is complex; however, the first intervention should be to prevent the vasospasm of RP that predisposes to development of DU. Avoiding triggers such as cold and psychological stress should be part of the management of all SSc patients with RP (Figure 2).[8] In addition, patients should be counseled to avoid behaviors that impact vasospasm, such as cigarette smoking. There are conflicting data regarding the impact of caffeine on RP, but excess caffeine should be avoided.

If a patient continues to have symptoms despite these interventions and lifestyle modifications, vasodilator therapy can be initiated. The first-line therapy for RP is dihydropyridine calcium channel blockers, which have been shown to modestly improve RP symptoms.[7] Experts recommend starting amlodipine at 5 mg daily and increasing to 10 mg daily in patients whose systemic pressures can tolerate the attendant hypotensive effects of this medication.[8] If this is ineffective or not tolerated due to systemic hypotension, selective serotonin reuptake inhibitors or local injection of botulinum toxin may be helpful, but have not been rigorously studied in SSc. Topical nitrates can also be tried. In certain refractory cases, additional vasodilator therapies used to treat pulmonary arterial hypertension may be useful. Phosphodiesterase type 5 (PDE-5) inhibitors have been studied and may be effective to decrease the frequency and duration of RP attacks, but are not approved for this indication in the United States.[9] Further, PDE-5 inhibitors cannot be used in combination with topical nitrates due to the risk of systemic hypotension. Data from studies conducted in Europe suggest effectiveness of intermittent intravenous prostacyclin infusions for severe cases, with durability of responses up to 4 weeks. However, this study was of intravenous iloprost, which is not available in the United States. Antiplatelet therapy may also be useful as an adjunct therapy. However, systemic anticoagulation is not recommended unless there is an underlying hypercoagulable state or an acute critical ischemic event.

For active DU, treatment options are similar as for RP, but include additional interventions. Instituting local therapy for the ulcer is imperative and should consist of washing the area with soap and water twice a day and placing a dressing over the wound after applying a topical antibiotic such as mupirocin. However, topical antibiotics should be stopped when the ulcer becomes dry as this may improve time to resolution of the DU. The wound should be assessed for infection. Systemic antibiotics effective against *Staphylococcus* and *Streptococcus* species should be instituted if infection is suspected; activity against methicillin-resistant *Staphylococcus aureus* should be considered and can be achieved with oral trimethoprim/sulfamethoxazole or clindamycin oral therapy.

Debridement may be required if necrotic tissue develops, but should be done with extreme caution given the underlying vascular compromise that extends beyond the area of necrosis. Pain control is often necessary; topical lidocaine (EMLA cream) can be used around the ulcer, but not in the ulcer. Nonsteroidal anti-inflammatory agents and/or low-dose narcotics may be necessary in certain cases. However, ongoing pain, particularly pain that extends beyond the boundaries of the ulceration, suggests persistent vasospasm, vessel occlusion, or macrovascular disease that requires more immediate evaluation.

Rarely, critical digital ischemia can occur and requires immediate medical attention. Blood flow to the digit should be addressed with external warming and vasodilator therapy should be maximized. Intravenous prostacyclins can be useful in this scenario and are usually dosed at 0.5-2 ng/kg/min for a 3- to 5-day course. Pain control needs to be addressed as well, as pain is a well-known stimulus for increasing sympa-

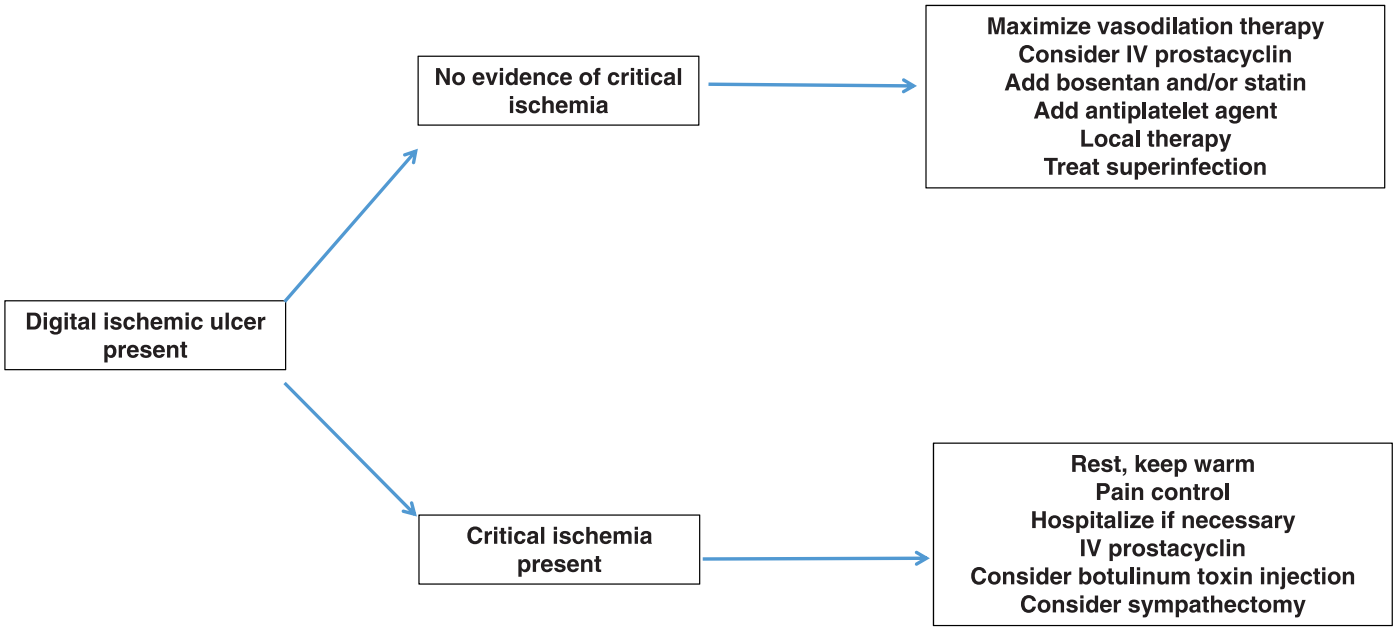



Figure 2.Proposed algorithm for management of digital ulcers. Critical ischemia (see Figure 1B).

thetic tone that can further exacerbate ischemia. Antiplatelet therapy along with anticoagulation should be considered based on the pathogenesis of this process, but there are no clinical trial data supporting this approach. Occasionally, surgical sympathectomy may need to be performed to reverse an acute crisis; this sympathectomy should be limited to the digital enervation as prior studies have demonstrated poor long-term outcomes for more proximal sympathectomy. Even with sympathectomy, there is a high risk of amputation (14% in a systematic review).[10] Combination of sympathectomy with local botulinum toxin injection may be an option as well, but requires further study.

Prevention of new DUs may be achieved with institution of medications. Endothelin receptor antagonists (ERA) such as bosentan and ambrisentan have been shown to reduce the incidence of new DUs in small studies. However, in a large randomized controlled trial of another ERA, macitentan, there was no significant difference in rate of new DU formation between treatment and placebo arms.[11] Whether this represents a failure of this particular agent or a class effect remains unknown. Statins may also reduce the number of new DUs and can be considered. Prostacyclins may also be used in this capacity.

In summary, DU presents a unique problem for patients with SSc. Digital ulcerations exert a significant impact on manual dexterity and health-related quality of life. Prevention of DU through management of RP is recommended, both with lifestyle modification and vasodilator therapies. Pulmonary arterial hypertension medications may be useful to treat refractory RP and may reduce the incidence of new DUs in certain patients. Critical digital ischemia is a medical emergency that requires a multidisciplinary approach to ensure best outcomes.

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