Management of Raynaud Phenomenon and Digital Ulcers in Scleroderma

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KEYWORDS

• Scleroderma • Raynaud phenomenon • Digital ischemia • Digital ulcer
• Prostacyclin • Calcium channel blocker • Thermoregulatory vessels

KEY POINTS

- The pathophysiology of Raynaud phenomenon (RP) and digital ulcers in scleroderma is complex, involving both vasospasm and structural disease of the vasculature.
- Therapy for RP and digital ulcers should involve both nonpharmacologic and pharmacologic treatments.
- Pharmacologic therapy for RP should include a combination of vasoactive agents that can reverse vasoconstriction and address biological pathways to prevent the progression of the underlying vasculopathy.
- Digital ulcers are a common complication of scleroderma vascular disease that requires both systemic and local tissue therapy.
- Critical digital ischemia is a medical emergency and requires urgent treatment. Multiple modalities are available to reverse an event and prevent digital loss.

BACKGROUND

Raynaud phenomenon (RP) is one of the most common clinical manifestations of scleroderma, experienced by 90% to 98% of patients, usually as the first symptom in the course of the disease (**Box 1**, **Table 1**).[1] The new 2013 classification criteria of the American College of Rheumatology (ACR)/European League Against Rheumatism (EULAR) now recognizes the importance of RP by including it as a feature to confirm a diagnosis of scleroderma.[2] RP often predates other symptoms and signs by several years, which suggests that the peripheral vasculature is the initial target of the scleroderma disease process.[3] The presence of RP alone is a clinical symptom

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Box 1
Key points for the management of digital ulcers

- Confirm that it is a digital ischemic ulcer and not another digital lesion
- Maximize vasodilatation
- Add other proven medications in addition to vasodilators
- Do not neglect local therapy
- Evaluate for and treat superinfection
- Evaluate for macrovascular disease, which can worsen digital ulcers

that is also a predictor of developing scleroderma. This concept is supported by studies finding that patients with a very early diagnosis of scleroderma already have RP.[4,5] Although a patient presenting with only RP, abnormal nail fold capillaries typical of scleroderma, and the presence of a specific scleroderma-related autoantibody do not meet the new ACR/EULAR criteria, studies do find that almost 80% of such patients develop scleroderma over subsequent years of follow-up.[6,7] A recent survey of anti-nuclear antibodies (ANA)-negative patients with scleroderma who did not have RP found that they often had a malignancy, suggesting that these patients may have a cancer-associated syndrome.[8]

To be diagnosed with RP, patients should experience episodic cold-induced or stress-induced sensitivity associated with pallor or cyanosis of the digits.[9] The pallor or cyanosis that accompanies the ischemic phase of an attack may be followed by erythema as a result of reactive hyperemia. Most patients do not experience all phases of color change: pallor, cyanosis, and erythema. The involvement of digital arteries, along with vasoconstriction of cutaneous arterioles, is responsible for the initial color change of pallor witnessed during RP.[10] When veins dilate and there is pooling of deoxygenated blood, the digits take on a cyanotic appearance. Patients with scleroderma are considered to have secondary RP and are more likely to experience digital ulceration and critical digital ischemia than patients with primary RP.[11] Patients with primary RP are less likely to have involvement of the thumb than patients with scleroderma.[12]

In both primary and secondary RP, there is increased reactivity of the blood vessels to cold and increased sympathetic tone. In vitro studies show that increased sympathetic tone is mediated by an increased expression of alpha-2c adrenergic receptors on smooth muscle of cutaneous arteries.[13] Exposure to cold leads to activation of the Rho/Rho-kinase signaling pathway and increased transport of alpha-2c receptors to the cellular membrane.[14] The translocation of these receptors is associated with increased cellular responsiveness to cold-induced adrenergic signals. Ex vivo studies of scleroderma blood vessel have shown that vascular smooth muscle of the arterioles display a selective increase in alpha2-adrenergic reactivity, suggesting that RP in scleroderma is in part caused by upregulation of the adrenergic receptors.[15] In scleroderma, there is also evidence of dysfunction of the endothelium resulting in an imbalance between vasoconstricting and vasodilatory stimuli.[16] Studies have suggested an overproduction of the vasoconstrictor endothelin-1[17] and an underproduction of the vasodilators nitric oxide and prostacyclin by the endothelial cells is involved RP of the peripheral blood vessels.[18]

In humans, the response of the cutaneous circulation to ambient temperature is critical to maintain a normal core temperature. Thermoregulatory vessels are present in

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