

## Sildenafil in the Treatment of Digital Ulcers in Patients with Systemic Sclerosis

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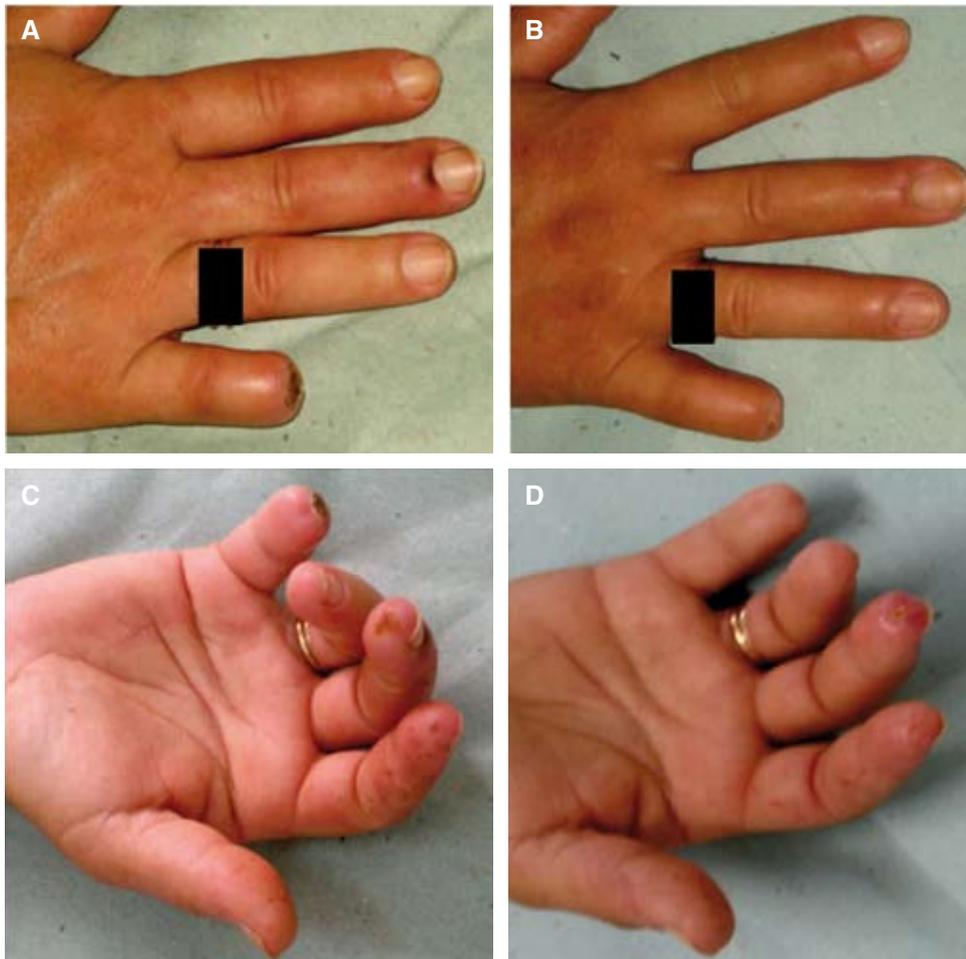
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### To the Editor:

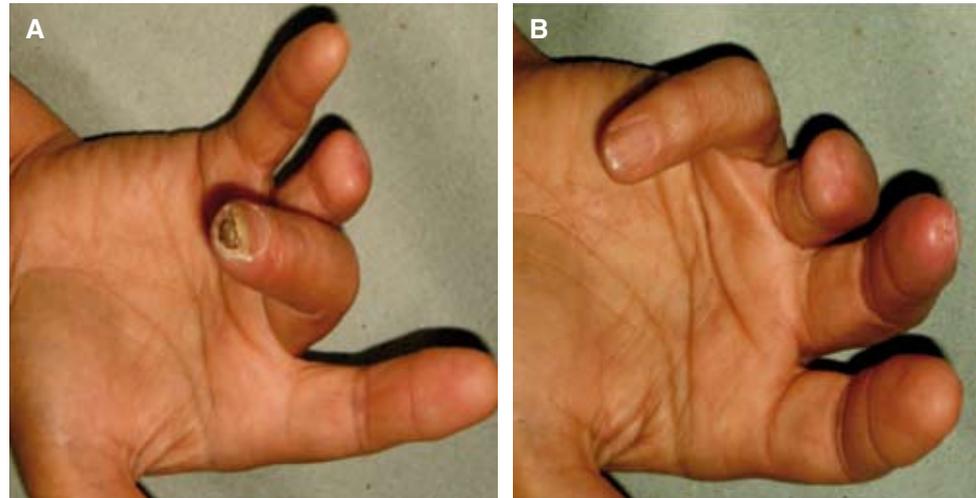
In systemic sclerosis, the collagen deposition, vasculopathy, and Raynaud phenomenon produce abnormalities in microcirculation that lead to ischemia, distal ulceration (DU) and, occasionally, necrosis of one or more phalanges.<sup>1</sup> We report 2 cases in which sildenafil was used as a treatment option.

The first case was a 46-year-old woman with a history of diffuse cutaneous systemic sclerosis diagnosed 4 years previously, who was receiving antiplatelet therapy and nifedipine. Four months earlier she presented DU with necrosis of the distal phalanx of the fifth finger on the right-hand, requiring amputation. The patient recently

attended presenting new DU on the third finger of the right-hand, with periungual hemorrhagic lesions but no signs of necrosis of the finger. On the fifth finger of the same hand, partial closure of the surgical scar could be observed on the amputation stump (Figure 1). The patient tested positive for antinuclear antibodies with a titer of 1:640 but negative for antiscleroderma (anti-Scl)-70 antibodies. Periungual capillaroscopy revealed enlarged capillaries, avascular areas and hemorrhages in the proximal nailfold. Given this situation, treatment was initiated with oral sildenafil 50 mg/d (in a single dose at night). A subjective improvement (reduction in number and intensity) of episodes of Raynaud phenomenon was



**Figure 1.** Appearance of the lesions (Case 1) before (A and C) and after (B and D) treatment with sildenafil.



**Figure 2.** Appearance of the lesions (Case 2) before (A) and after (B) treatment with sildenafil.

achieved with complete recovery of the finger pad on the affected finger, disappearance of the ischemic and hemorrhagic lesions, and complete closure of the surgical wound 60 days after treatment was started (Figure 1). A year later the patient presented serious renal insufficiency, and was admitted to the intensive care unit where she later died.

The second case was a 63-year-old woman diagnosed 2 years ago with limited cutaneous systemic sclerosis and a recent history of gastroesophageal reflux. Treatment was initiated with antiplatelet drugs, ranitidine, and calcium channel blockers, which exacerbated the digestive symptoms and were therefore replaced with pentoxifylline. A year previously she had developed necrosis of the distal phalanx of the ring finger, requiring amputation. The patient consulted for DU on the finger pad of the third finger of the right-hand, with signs of ischemia and necrosis, associated with subungual hemorrhage, edema, and erythema on the distal phalanx of the same finger (Figure 2).

She tested positive for antinuclear antibodies with a titer of 1:320 with positive anticentromere antibodies. Periungual capillaroscopy revealed megacapillaries and avascular areas. Treatment was initiated with oral sildenafil 50 mg/d (in a single dose at night), obtaining subjective improvement in the episodes of Raynaud phenomenon and complete healing of the lesion in 60 days (Figure 2). Twenty months later she began to experience dyspnea, and an echocardiograph showed indirect signs of moderate pulmonary hypertension.

Raynaud phenomenon and DU are common in patients with systemic sclerosis.<sup>1,2</sup> Treatment includes local and general measures: the application of antiseptics and debridement of wounds; and avoidance of exposure to cold and drugs that induce vasospasm, giving up smoking, and adequate use of analgesia, respectively.<sup>2,3</sup> Where there

are serious lesions, vasodilator treatment should be started with calcium channel blockers, associated with antiplatelet treatment and heparin at anticoagulant doses.<sup>2,3</sup> In serious and persistent digital ischemia, benefits have been seen in the use of prostacycline analogs such as intravenous alprostadil, iloprost, or epoprostenol.<sup>3</sup> Bosentan (an endothelin-receptor antagonist) has proven effective in the prevention of further DU.<sup>4</sup>

Recently improvements in DU have been reported when using sildenafil in patients with primary and secondary Raynaud syndrome.<sup>5-9</sup> As drugs such as iloprost and epoprostenol are not available in our hospital, we used sildenafil in both cases. We followed the therapeutic regimen first outlined by Lichtenstein<sup>5</sup> for the treatment of Raynaud syndrome and DU. In both cases the DU resolved rapidly, with good tolerance and no adverse effects. An increase of oxidative stress associated with a deficit in nitric oxide is one of the factors involved in the pathogenesis of microvascular abnormalities and in wound-healing mechanisms.<sup>1,10</sup> The inhibition of 5-phosphodiesterase mediated by sildenafil results in the accumulation of cyclic guanosine monophosphate (cGMP), leading to a reduction in intracellular calcium that produces relaxation of the vascular smooth muscle and therefore vasodilation.<sup>3</sup> This type of inhibition prevents the breakdown of cGMP, increasing the effects of nitric oxide on the endothelium—a phenomenon that constitutes an attractive proposal in the treatment of DU in systemic sclerosis.<sup>9</sup> Early intervention of this type could provide benefits without producing major adverse effects when used with caution in patients with arterial hypertension; it is contraindicated in patients on treatment with nitrates. In terms of dosage, the duration of treatment with sildenafil has varied, though it is usually given for at least 4 weeks, and doses of 50 mg/d or every 12 hours are used.<sup>7-9</sup>

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**Conflicts of Interest**

The authors declare no conflicts of interest.

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