Case Report

Severe Refractory Fingertip Ulcerations in a Patient with Scleroderma: Successful Treatment with Sildenafil

CHRISTOPHER LEE COLGLAZIER, PAUL G. SUTEJ, and KENNETH S. O'ROURKE

ABSTRACT. Systemic sclerosis (scleroderma) is a multisystem fibrotic disease that commonly manifests with severe Raynaud's phenomenon and slow-healing cutaneous ulcerations. Reduced nitric oxide levels have been proposed to play a role in the pathogenesis of vascular disease in scleroderma, and therefore sildenafil (which increases nitric oxide levels) is an attractive therapeutic prospect. We describe a patient with limited cutaneous systemic sclerosis who presented with severe nonhealing finger ulcerations despite conventional management, who showed marked improvement with oral sildenafil. (J Rheumatol 2005;32:2440–2)

Key Indexing Terms:
SCLERODERMA SYSTEMIC SCLEROSIS
ULCERATION SILDENAFIL CUTANEOUS

Systemic sclerosis (scleroderma) is a multisystem fibrotic disease resulting in a spectrum of complications including sclerodactyly, Raynaud's phenomenon, pulmonary fibrosis, pulmonary hypertension, esophageal dysmotility, and renal failure. The etiology is not well defined, and proposed mechanisms have included genetic susceptibility, immune activation, vascular alteration, and fibroblast proliferation[1]. All the proposed pathways end in collagen deposition and vascular damage.

In affected blood vessels, the combination of collagen deposition and vasoreactivity can lead to blood vessel occlusion and tissue necrosis of the supplied organ. In the hands, this results in Raynaud's phenomenon, and can cause ulcerations that are commonly nonhealing and may lead to amputation. Studies of affected blood vessels have revealed increased concentrations of vasoconstrictive factors such as endothelin-1[2], as well as increased levels of proinflammatory intracellular and lymphocyte adhesion molecules[3]. An additional proposed contributing factor to the vasculature sequela in scleroderma is deficient levels of nitric oxide, a potent vasodilator. Nitric oxide is released by, and depends on, healthy vascular endothelium. Although the data are controversial, damaged endothelium in scleroderma may lead to a decrease in the release of nitric oxide[4].

From the Section on Rheumatology and Immunology, Department of Internal Medicine, Wake Forest University Baptist Medical Center, Winston Salem, North Carolina, USA.

C.L. Colglazier, MD, Fellow; P.G. Sutej, MD, Associate Professor; K.S. O'Rourke, MD, Associate Professor, Section Head, Rheumatology and Immunology.

Address reprint requests to Dr. C.L. Colglazier, 760 Maidstone Ct., Cincinnati, OH 45230. E-mail: leecolglazier@hotmail.com

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The mechanism of increasing endogenous nitric oxide levels by inhibition of phosphodiesterase-5 makes sildenafil an attractive prospect for the treatment of scleroderma. While a randomized trial of sildenafil among patients with nonscleroderma Raynaud's phenomenon did not show a benefit[5], case reports of improved peripheral blood flow with sildenafil in a scleroderma patient[6], and in both scleroderma related and nonscleroderma related digital ischemia[7] have been encouraging. Positive case reports of the use of sildenafil in scleroderma led us to use it in a scleroderma patient with severe finger ulcerations.

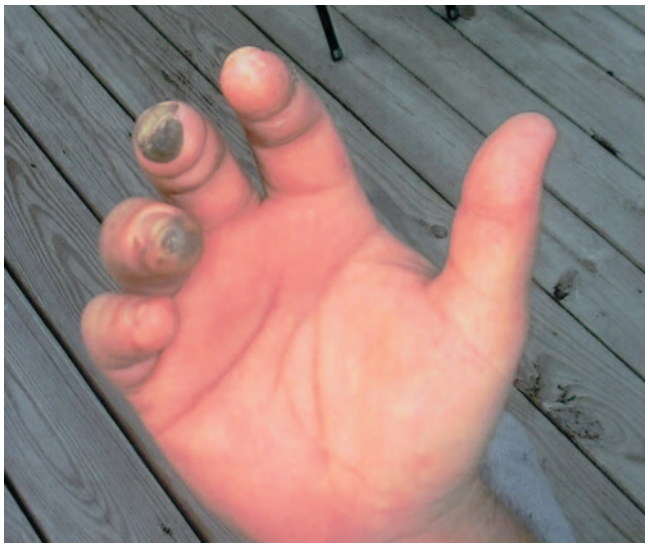
CASE REPORT

A 31-year-old man presented with an 18 month history of severe Raynaud's phenomenon, skin tightening of the fingers and face, telangiectasias, gastroesophageal reflux, and nonhealing fingertip ulcerations. Physical examination revealed sclerodactyly distal to the proximal interphalangeal joints, facial sclerosis, and diffuse telangiectasias. There were multiple ulcerations of the fingertips, the largest a 1 cm ulceration at the tip of the right fourth finger (Figure 1). He was diagnosed with limited cutaneous systemic sclerosis.

Laboratory data revealed a positive antinuclear antibody (titer ≥ 1280, nucleolar pattern), a negative anti-Scl-70 antibody, and negative anticentromere antibody. A chest radiograph revealed no definite evidence of pulmonary fibrosis. Pulmonary artery pressure from a transthoracic echocardiogram could not be measured. Invasive arteriograms of both upper extremities revealed an absent palmar arch of both hands and severe truncation of vessels in all fingers, with no visible vessel past the middle phalanx.

Initial treatments included smoking cessation 8 months prior to his first visit with us. One month prior to his first visit he was also given nifedipine 10 mg twice a day, aspirin 81 mg once a day, and pentoxifylline 400 mg 3 times a day. We continued this regimen for one more month; however, he continued to experience worsening of fingertip ulcerations, Raynaud's phenomenon, and significant hand pain.

Sildenafil 50 mg per day was then added to his regimen. He initially experienced symptoms of hypotension, and therefore nifedipine was discontinued and the sildenafil dose was reduced to 25 mg per day. After one



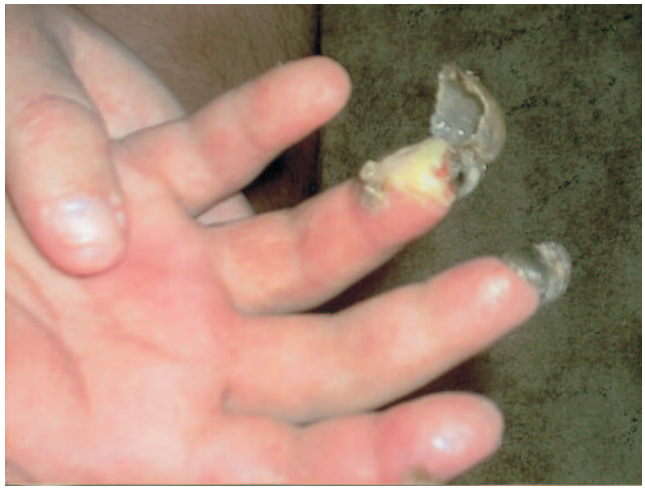


Figure 1. Finger ulcerations prior to sildenafil therapy.

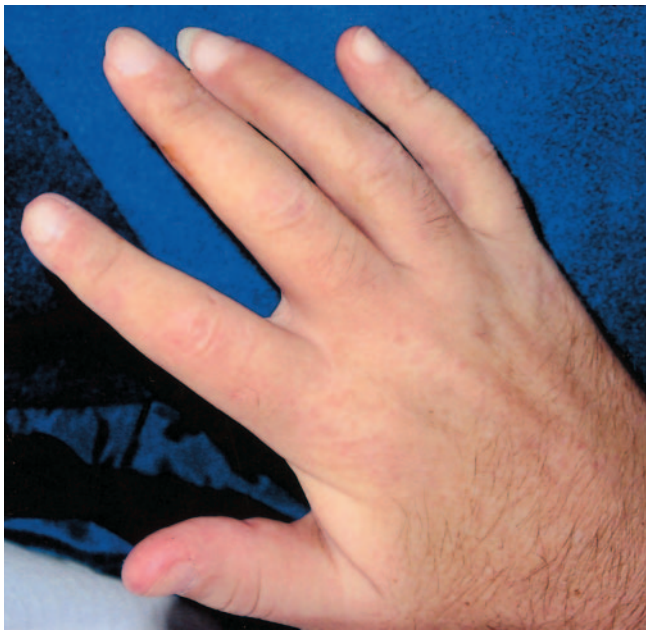
week, the dose was returned to 50 mg per day, which he tolerated. The rest of his medical regimen remained unchanged, except for a brief trial of methotrexate, which was discontinued due to side effects.

Over the next 3 months, he experienced gradual healing of his finger ulcerations. By 4 months, his ulcerations were completely healed, with only slight residual distal eschar (Figure 2). The frequency of Raynaud's phenomenon decreased, hand pain decreased, and overall quality of life measured by a visual analog scale improved.

DISCUSSION

Conventional treatment of Raynaud's phenomenon and finger ulcerations in scleroderma, including hand warming, calcium channel blockers, and topical nitroglycerin, are often ineffective. In a randomized trial, epoprostenol showed a trend to improvement in Raynaud's phenomenon, but no change in ulceration rates[8]. In addition, epoprostenol is invasive, associated with significant side effects, and expensive, and is normally reserved for patients experiencing symptomatic pulmonary hypertension. Although bosentan was shown in a randomized trial to prevent new ulceration in scleroderma[9], the study failed to show a difference in ulcer healing rates, and bosentan is also normally reserved for use in pulmonary hypertension. Surgical sympathectomy can be effective for Raynaud's phenomenon and finger ulcerations; however, it is invasive and patients do not always respond.

Sildenafil is an attractive prospect for treatment of scleroderma related Raynaud's phenomenon and finger ulcerations given its ease of administration and relatively nontox-



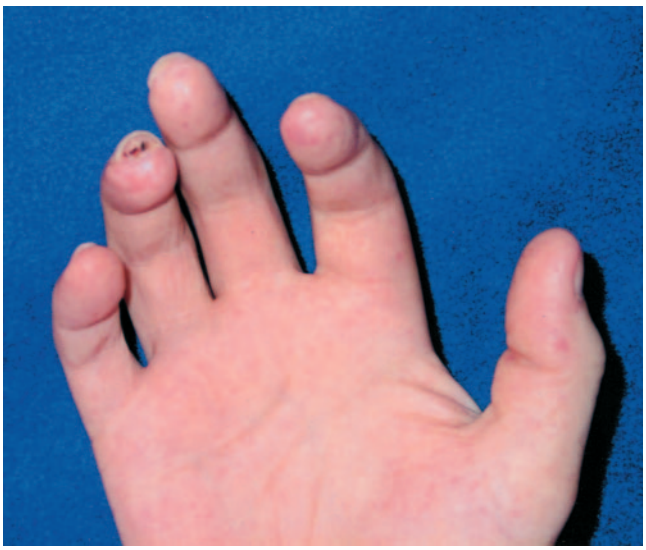


Figure 2. Healed fingertip ulcerations after 4 months of sildenafil 50 mg per day.

ic profile. The data on its use in vascular disease in general is growing, such as its efficacy in nonscleroderma pulmonary hypertension[10]. A case report of improvement in a scleroderma patient with respect to pulmonary hypertension and peripheral blood flow is encouraging for a condition with little proven therapy[5]. Experience with its use in scleroderma remains limited but is growing. We are encouraged by our patient's initial response. While it likely does not treat the underlying cause of scleroderma, it may be a useful medication to relieve symptoms, help heal cutaneous ulcerations, and possibly postpone surgical intervention. However, well designed controlled trials are needed to further define a causative relationship, and to establish proper dose and duration measures.

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