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Case Report

Successful Treatment of Newly Developed, Intractable Digital Ulcers and Gangrene with Bosentan in Systemic Sclerosis

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In systemic sclerosis, digital ulcers and gangrene are somewhat common clinical characteristics of obliterative vasculopathy. These manifestations increase morbidities, such as pain, infections, and acroosteolysis. However, patient responses to the appropriate treatments are often inadequate. We treated a patient with systemic sclerosis who had a refractory digital ulcer and gangrene with bosentan, an endothelin receptor antagonist, and observed improvement. Here we systematically review this case. **(J Rheum Dis 2016;23:193-197)**

Key Words. Bosentan, Systemic scleroderma, Gangrene

INTRODUCTION

Systemic sclerosis is a rare systemic connective tissue disease that results in blood vessel damage, skin fibrosis, and invasion of internal organs. The pathophysiological abnormalities of this disease are characterized by abnormal capillaries, an impaired immune system, and excess collagen deposition [1].

Vascular lesions play an important role in tissue damage and the etio-pathogenesis of systemic sclerosis. Raynaud's phenomenon is often observed in the early stage of the disease and may progress to digital ulcers (DUs) or digital gangrene if this phenomenon repeats chronically. DUs are seen in about 40% to 50% of all patients with systemic sclerosis; these ulcers can cause severe pain, impaired finger function, and secondary infections due to delayed healing [2]. Even if the ulcers heal, 31% to 71% of patients have been shown to relapse [3]. The etiologies of DUs have been suggested to include impaired afferent vasomotion, microvascular disruption, reduced venous drainage, increased local platelet activation, and increased leukocyte adherence [4].

DUs are often unresponsive to treatments, and no clear therapeutic guidelines exist at present. Here we report a case of improvement after bosentan treatment of a patient with systemic sclerosis who developed DU and gangrene refractory to other treatments.

CASE REPORT

Past history and present illness

A 45-year-old female visited Kosin University Gospel Hospital due to DU and pain in her right middle finger. The patient had been diagnosed with diffuse systemic sclerosis three years ago, when she presented with Reynaud's phenomenon; skin thickening of the hands, forearms, and back; and pulmonary fibrosis of the bilateral lower lobes. She was administered nifedipine, ramipril, and colchicine. The patient completed six intravenous (IV) cyclophosphamide treatments for interstitial lung disease (ILD), which accompanied her systemic sclerosis, until one month prior to the development of DUs. No additional immunosuppressive agents were used. An ulcer suddenly developed at the tip of the third

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finger of her right hand in the absence of any specific trauma history. Over-the-counter ointment was used, but her pain and ulceration worsened, causing the patient to come to the hospital. She has a ten pack-year smoking history and currently smokes five cigarettes a day; she does not drink alcohol.

Physical examination

At her physical exam at the first visit after the development of the DU, her vital signs were: blood pressure, 110/70 mmHg; pulse, 78 beats/min; respiration rate, 20 breaths/min; and body temperature, 36.7°C. Hardening of the skin was noted from her finger to forearm. In the finger with the ulcer, overall swelling, local tenderness, and erythema were observed (Figure 1A).

Laboratory test findings

Her test results at the time of admission were as follows: white blood cell 5,400/mm^3 (neutrophils 44.2%, lymphocytes 39.3%, monocytes 14.2%, eosinophils 1.7%, and basophils 0.6%), 11.2 g/dL hemoglobin, 32.1% hematocrit, and 253,000/mm^3 platelets, suggesting mild anemia. Her lipid profile was within the normal limits, with 120 mg/dL total cholesterol, 70 mg/dL low density lipoprotein-cholesterol, and 62 mg/dL triglycerides; however, her high density lipoprotein-cholesterol level was decreased (24.7 mg/dL). Her C-reactive protein level and erythrocyte sedimentation rate were both elevated at 3.5 mg/dL (normal range 0 to 1 mg/dL) and 73 mm/h (normal range 1 to 20 mm/h), respectively. Her liver function, renal function, and urinalysis test results were all within their normal limits. Autoantibody tests revealed that she was positive for antinuclear antibodies (1:160), but negative for anti-dsDNA antibodies, anti-Sm antibodies, anti-centromere antibodies, and anti-topoisomerase I antibodies. Her test results for rheumatoid

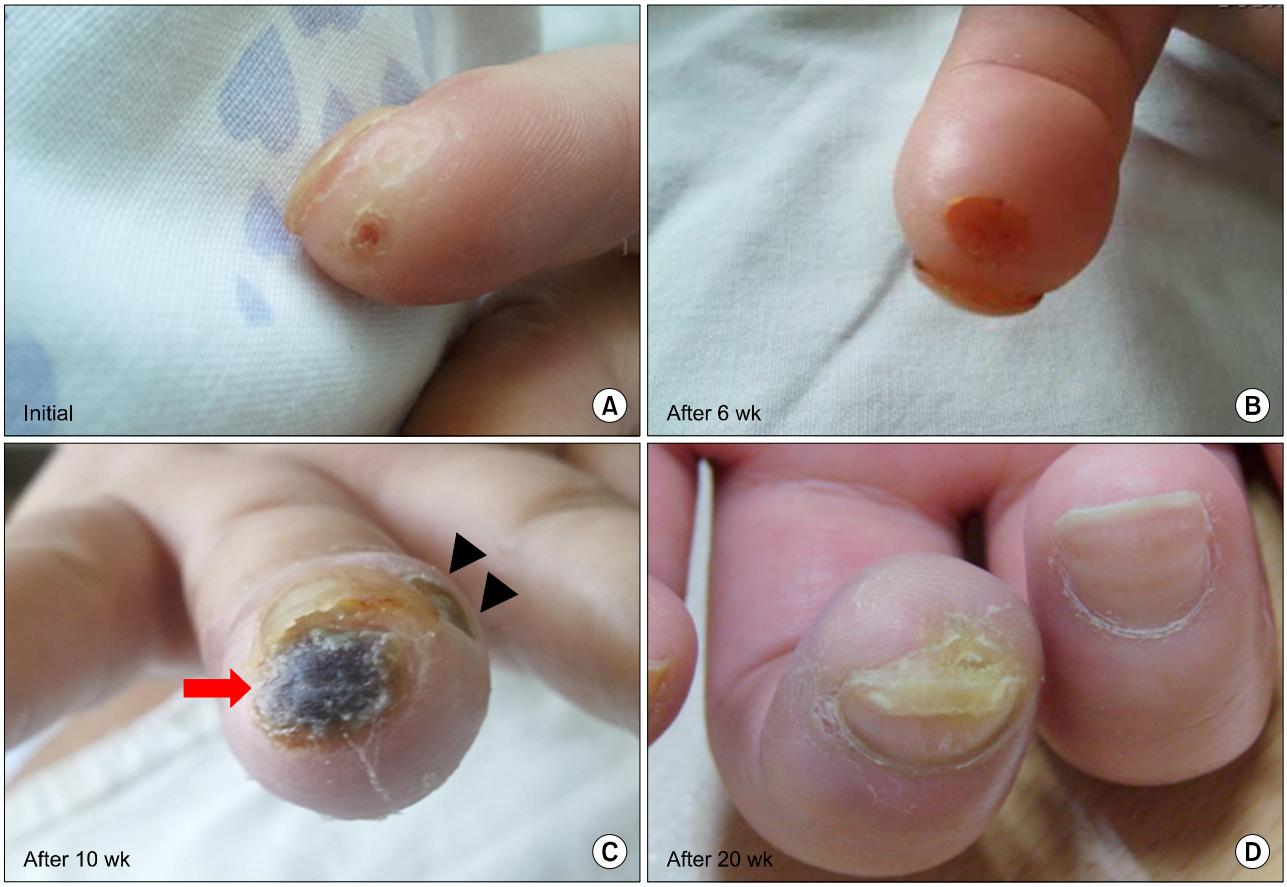

Figure 1. Clinical course of digital ulcer. (A) An ulcer with pain had developed on the tip of her right middle finger by her first visit. (B) Six weeks after the first visit, despite using beraprost, the ulcer had worsened. Her treatment was switched to intravenous alprostadil. (C) Ten weeks after the first visit, the fingertip ulcer had deteriorated to gangrene (red arrow), despite the use of alprostadil for four weeks. Moreover, a new ulcer on the lateral side of the finger was noted (arrowhead). At this time, alprostadil was switched to bosentan. (D) Her digital ulcers and gangrene had improved after 10 weeks of bosentan treatment.

factor, anti-cyclic citrullinated peptide antibodies, anti-neutrophil cytoplasmic antibodies, anti-cardiolipin antibodies, and lupus anticoagulant were all negative.

Imaging studies

The X-ray results of her hands were unremarkable. A bone scan revealed an increased isotope level at the tip of her right middle finger (Figure 2).

Echocardiographic study

An echocardiogram acquired on admission showed a tricuspid regurgitation maximal velocity of 3.03 m/s and a right ventricular systolic pressure of 47 mmHg, suggesting pulmonary arterial hypertension; however, the patient did not have dyspnea.

Treatment and clinical progress

After the DU was confirmed, beraprost, a synthetic analogue of prostacyclin, was used (in addition to home medications, nifedipine, ramipril, and colchicine). To prevent secondary infection, an antibiotic ointment was also used. Six weeks later, her skin ulcers had worsened (Figure 1B), and the patient was admitted for four weeks to receive intravenous alprostadil, a synthetic analogue of prostaglandin (PG)E_1. *Enterobacter cloacae* was identified in a culture from the skin lesion. Skin disinfection and antibiotic treatment (levofloxacin) were both carried out. However, despite continuous treatment, the ulcer progressed to skin gangrene and a new skin ulcer developed in the lateral side of the finger (Figure 1C). Alprostadil was determined to be ineffective and her regimen was

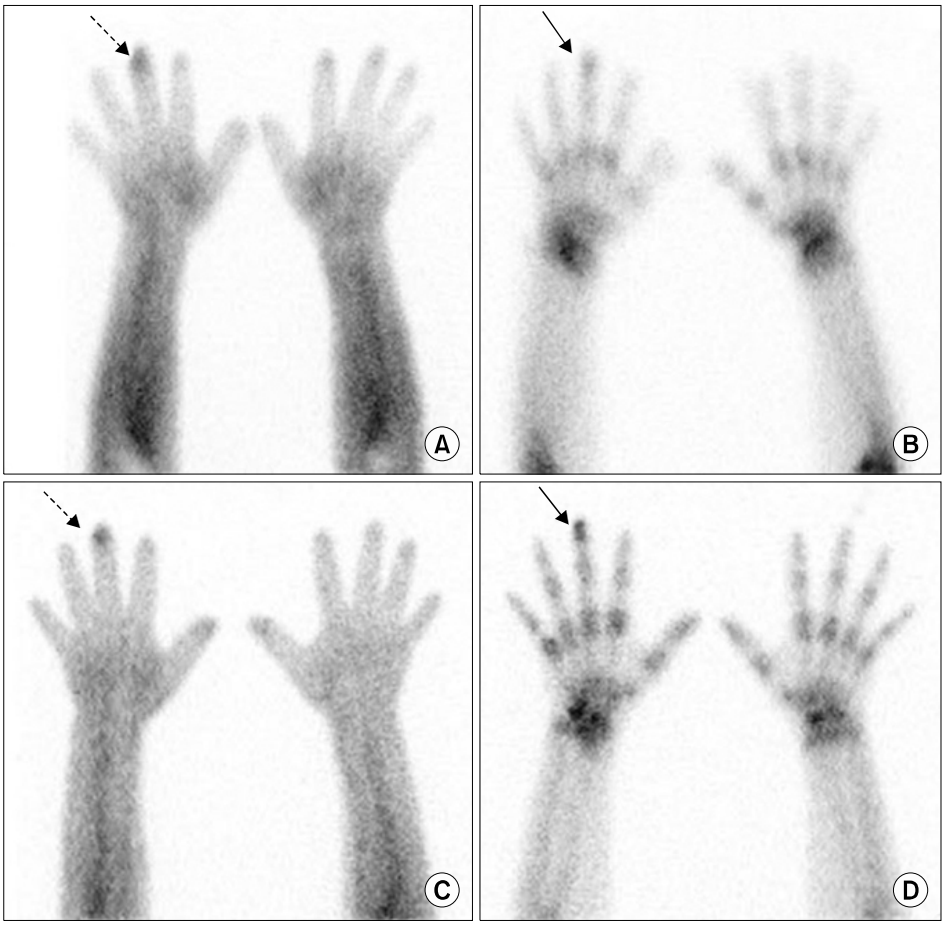

Figure 2. Three phase bone scan of both hands. (A, B) Blood pool activity and delayed 3-phase bone scan images at the time when the initial digital ulcer was noted. Localized increased blood pool activity was observed in the distal portion of the right third digit (A, dotted arrow). Minimally increased uptake was visible at the distal phalanx of the right third digit on the delayed image (B, arrow), which might have been caused by secondary hyperemia due to the soft tissue ulcer. (C, D) At the time of the 2-month follow-up 3-phase bone scan, the patient's symptoms were worsening. The localized blood pool activity of the right third digit was more intense (C, dotted arrow). At this time, prominent uptake was noted in the distal phalanx of the right third digit on the delayed image (D, arrow). This finding suggested the possibility of osteomyelitis of the distal phalanx of the right third digit.

switched to bosentan (125 mg/d). About two weeks after starting bosentan, the lesions had not worsened, and the patient was discharged to continue treatment as an outpatient. About eight weeks after discharge, her DUs appeared to be almost resolved (Figure 1D). The patient is currently on ramipril (5 mg/d), colchicine (0.6 mg/d), and bosentan (125 mg/d). The patient is currently maintained at a stable state, without any DU recurrence, and is being observed as an outpatient.

DISCUSSION

Systemic sclerosis is a systemic connective tissue disease that is characterized by vasculopathy and progressive fibrosis of the skin and internal organs. Endothelial and vascular damage, as well as activation of fibroblasts, play important roles in the pathophysiology of this disease [1]. Vasculopathy can affect vessels of various sizes, causing microvascular lesions such as capillary vessel damage, as well as macrovascular lesions such as pulmonary artery hypertension. DU is a common complication observed in patients with systemic sclerosis. The main risk factors of DU development include diffuse systemic sclerosis, early onset of Raynaud's phenomenon, a high Rodman's skin score, and anti-topoisomerase I antibodies [5]. Moreover, smoking is also known to increase the risk of DU complications [6].

In this case, the patient exhibited a known risk factor for DUs (ILD) and also had a high risk of DU complications due to her smoking history. During conventional treatment (nifedipine and ramipril) for Raynaud's phenomenon, her DU was first noted. Synthetic PG analogues (beraprost and alprostadil) were used but did not yield a response, and her DU progressed to digital gangrene. However, bosentan treatment yielded clear improvements of her DU.

No clear guidelines have yet been established for the treatment of systemic sclerosis-related DUs. In general, both nondrug and drug treatments are carried out, and if these options do not yield any response, surgical treatments are considered. Background therapies include avoiding exposure to cold, minimizing fingertip damage, frequently using moisturizer to minimize skin dryness, and avoiding vasoconstricting drugs such as nicotine and narcotics. As a basic drug treatment, antibiotics for secondary infection and anti-inflammatory drugs to control pain are used, although definitive evidence supporting this treatment is lacking.

Specific treatments for DUs include PG analogues, calcium channel blockers, angiotensin-converting enzyme inhibitors, vasodilators (e.g., phosphodiesterase [PDE]-5 inhibitors), and endothelin (ET) receptor antagonists (ERAs) (e.g., bosentan) [7,8]. Of the available PG analogues, a few studies have reported treatment benefits of IV alprostadil (PGE_1) and IV iloprost (PGI_2) for systemic sclerosis-induced ischemic ulcers [9,10]. However, most studies about PG analogues have focused on Raynaud's phenomenon rather than DUs. Two well-designed, randomized controlled trials have investigated the efficacy of bosentan in treating DUs. Randomized Placebo-controlled studies on the prevention of Ischemic Digital ulcers in Scleroderma (RAPIDS-1 and RAPIDS-2) reported that bosentan helps prevent the emergence of new DUs [11,12]. In a retrospective French study, bosentan was shown to help prevent DUs in severe, refractory, ongoing ulcerative disease [13]. Moreover, a recently published meta-analysis concluded that PDE-5 inhibitors are effective in healing DUs, and that bosentan and IV iloprost help prevent new DUs [14]. However, this analysis was limited by a small sample size and few comparative studies.

In patients with systemic sclerosis, plasma ET concentrations are increased, and ET_B receptor expression is elevated in the lungs, skin, and blood vessels. ET has been shown to mediate blood vessel endothelium proliferation and blood vessel constriction [15]. Currently, ET receptor antagonists such as bosentan are widely used to treat pulmonary artery hypertension resulting from systemic sclerosis. This observation indirectly suggests that these antagonists can also be used to treat small vessel lesions related to skin ulcers. Bosentan has been shown to be effective in preventing new DU recurrence, but has not typically been used to treat existing DUs. However, in this case, bosentan was very effective in treating refractory DUs. Although more clinical evidence in support of this observation is still needed, this case provides some strong preliminary evidence. Thus, future studies should explore the potential of bosentan to treat existing ulcers. Also, this case indicates that bosentan may be a good option before considering surgical treatment for DUs nonresponsive to other drugs.

SUMMARY

No clear guidelines have been established for treating systemic sclerosis-related DUs, and the efficacies of po-

tentially appropriate drugs are unknown. Although bosentan, an ERA, was recently shown to be effective in preventing new DU recurrence, its ability to treat existing DUs had not been demonstrated. In this case, clear improvements were observed after the use of bosentan to treat a newly developed DU and gangrene refractory to other treatments. Future studies focusing on the role and efficacy of bosentan have the potential to be highly informative.

CONFLICT OF INTEREST

No potential conflict of interest relevant to this article was reported.

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