

# Basic Fibroblast Growth Factor Treatment for Skin Ulcerations in Scleroderma

Kei-ichi Yamanaka, MD; Tomoko Inaba, MD; Eriko Nomura, MD; Daniel Hurwitz, MD; David A. Jones, MD; Arata Hakamada, MD; Kenichi Isoda, MD; Thomas S. Kupper, MD; Hitoshi Mizutani, MD

*We report the use of topical application of recombinant human basic fibroblast growth factor (rhbFGF) to successfully treat therapy-resistant, chronic leg ulcers in scleroderma. Endothelial cell FGF receptors are directly stimulated by bFGF; also, bFGF promotes the regeneration of capillary-rich granulation tissue. We conclude that topical bFGF may be a powerful new pharmacologic tool for treating severe skin ulcers.*

*Cutis.* 2005;76:373-376.

**L**eg ulcers are a common and difficult complication in many connective tissue diseases.<sup>1</sup> In patients with connective tissue diseases, even minor trauma to the legs commonly results in leg ulcers resistant to therapy. We report a patient with systemic sclerosis–dominant overlap syndrome and recalcitrant skin ulcers on both legs. The patient underwent 5 years of unsuccessful treatment using many different approaches, including 3 skin grafts and systemic and local therapies. Recently, the importance of growth factors in wound healing has become obvious, and topical recombinant human basic fibroblast growth factor (rhbFGF) has been introduced for clinical application. bFGF directly stimulates FGF receptors on the fibroblasts and the endothelial cells<sup>2</sup>; additionally, it strongly promotes proliferation of fresh, capillary-rich granulation tissue in the wounds. Marked fibrosis and deposition of collagenous tissue characterize scleroderma and related diseases. These diseases also are characterized by overproduction of growth factors including transforming growth factor  $\beta$ , connective tissue growth



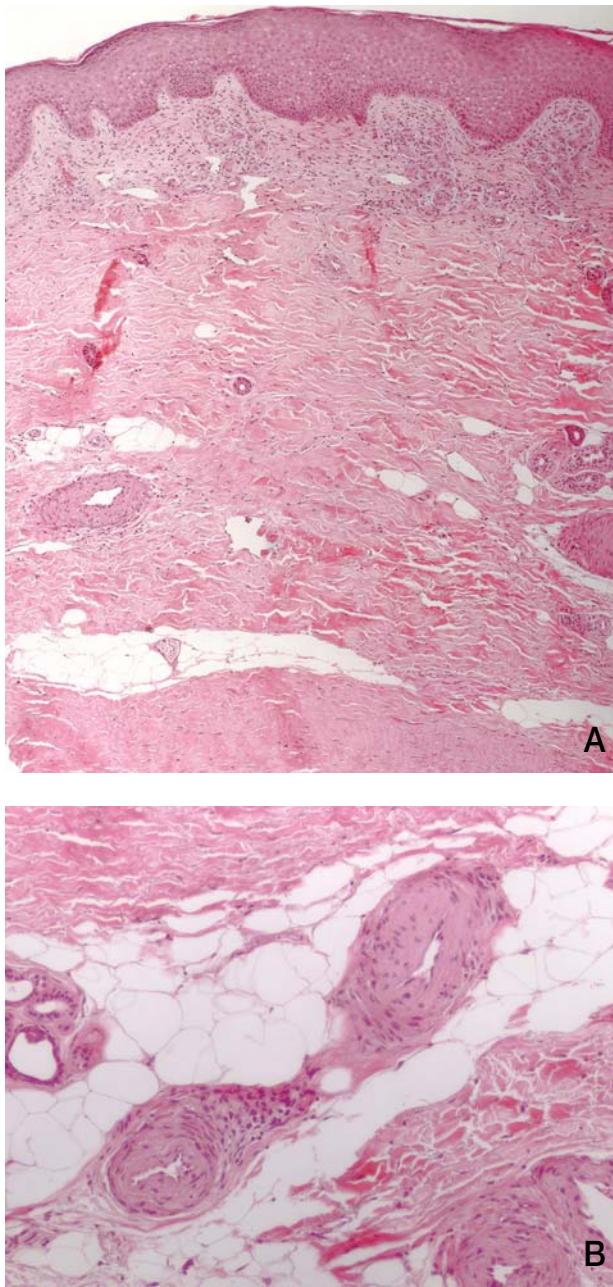
**Figure 1.** Multiple skin ulcers in systemic sclerosis–dominant sclerotic skin. The ulcers were fingertip sized, appeared deep and punched out, and were covered with necrotic tissue.

factor, platelet-derived growth factor, and FGF. Therefore, we were concerned of the risk of aggravating the preexisting fibrosis of scleroderma in our patient with the application of topical rhbFGF; however, all the patient's ulcers were reepithelialized within 20 days after starting therapy, and no visible recurrence developed during the 20-month follow-up period. This treatment is potentially an important new approach for recalcitrant skin ulcers in the setting of autoimmune collagen diseases.

Accepted for publication February 28, 2005.

Drs. Yamanaka, Inaba, Nomura, Hakamada, Isoda, and Mizutani are from the Department of Dermatology, Mie University, Graduate School of Medicine, Japan. Drs. Yamanaka, Hurwitz, Jones, and Kupper are from the Department of Dermatology, Harvard Skin Disease Research Center, Brigham and Women's Hospital, Boston, Massachusetts.

Reprints: Kei-ichi Yamanaka, MD, Department of Dermatology, Mie University, Graduate School of Medicine, 2-174 Edobashi, Tsu, Mie 514-8507, Japan (e-mail: yamake@clin.medic.mie-u.ac.jp).



**Figure 2.** The deep dermis is replaced with thick hyalinized collagen bundles, and there is a superficial perivascular lymphocytic infiltrate. The epidermis is atrophic and sweat glands are entrapped by expanded dermal fibrous tissue. Vessels proliferate in the papillary dermis (A). The lumen of the arteries in the deep dermis is narrow (B)(H&Es, original magnifications  $\times 40$  and  $\times 100$ ).

### Case Report

A 45-year-old woman with multiple skin ulcers on both shins and insteps presented to the dermatology clinic of Mie University Hospital, Japan. She had an 11-year history of overlap syndrome that included



**Figure 3.** Vessels of the legs with marked calcification, which forms a weblike pattern on x-ray.

systemic sclerosis, polymyositis, and systemic lupus. Except for the sclerosis of her skin, the patient's systemic manifestations had been well controlled by oral cyclosporine 100 mg daily and prednisolone 10 mg daily. The multiple skin ulcers first appeared on the sclerotic skin of her legs 6 years prior to presentation. The ulcers were fingertip sized, appeared to be deep and punched out, and were covered with necrotic tissue (Figure 1). The fascia and tendon sheaths in the ulcers were necrotic at the initial presentation and were removed surgically.

Histologically, the deep dermis was replaced with thick hyalinized collagen bundles, and there was a superficial perivascular lymphocytic infiltrate. The epidermis was atrophic, and sweat glands were entrapped by expanded dermal fibrous tissue. Vessels proliferated in the papillary dermis (Figure 2A). The lumen of the arteries in the deep dermis is narrow (Figure 2B). Therefore, both arterial and venous





**Figure 4.** All ulcers completely reepithelialized within 20 days after starting treatment with recombinant human basic fibroblast growth factor.

changes were involved in the pathogenesis of the ulcers in the present case. Results of a radiologic examination revealed the vessels of the patient's legs had marked calcification, which formed a weblike pattern (Figure 3).

We believe that the severely impaired dermal and subcutaneous circulation of the patient was making her ulcers highly resistant to therapy. Because of the presence of chronic venous insufficiency, we prescribed a compression dressing using stockings and elastic bandages; however, this treatment did not improve the lesions. Intravenous and topical prostaglandin  $E_1$  also were not effective.

Additionally, 3 attempts to apply split-thickness skin grafts were unsuccessful, with none of the skin grafts surviving despite the absence of signs of infection. Of note, systemic manifestations during this period were well controlled. Laboratory findings, including erythrocyte sedimentation rate, C-reactive protein level, and anti-double-stranded DNA antibody titer, were all within reference range.

The patient was started on a new therapeutic regimen that consisted of 30  $\mu\text{g}$  of rhbFGF topically applied to the wounds daily in combination with prostaglandin  $E_1$  ointment. Before application of rhbFGF, necrotic tissue was surgically removed, and the ulcers were cleansed with sterile saline. Next, the rhbFGF solution (0.1% in saline) was sprayed onto the lesions, which were then covered with 2 g of 0.003% prostaglandin  $E_1$  ointment and dressed with sterile gauze sheets. Within 10 days of starting treatment, proliferating pink granulation filled the ulcerative lesions. Within 20 days, the lesions were completely reepithelialized (Figure 4). The ulcers did not recur during the 20-month follow-up period. No wound-healing abnormalities or exacerbation of scleroderma were identified.

#### Comment

Recalcitrant skin ulcers are a common complication in connective tissue diseases. The prevalence rate of leg ulcers in patients with systemic sclerosis is as high as 50% or more.<sup>3</sup> In healthy individuals, wound healing advances step-by-step through hemostasis, inflammation, propagation, and then restructuring. Various inflammatory cells, cytokines, and growth factors play specific roles in each step.

Some fibrous connective tissue diseases are characterized by impaired wound healing. The precise mechanisms underlying fibrotic changes and ulceration are still obscure, but impaired circulation, infection, and disease-induced changes in mechanical pressure have been proposed as causative factors. Surgical treatments for major arterial and venous insufficiency, including bypass grafting, percutaneous transluminal angioplasty, and saphenectomy, have been used; however, these treatments have high surgical complication rates and poor success rates.

Multiple cytokines and growth factors play an important role in wound healing. Representative growth factors include transforming growth factor  $\beta$ , connective tissue growth factor, platelet-derived growth factor, and bFGF. These growth factors have pluripotential biologic activities aside from growth regulation of fibroblasts in wound healing.<sup>4</sup> Expression of these growth factors elevates during the wound healing process.<sup>5</sup> Topical application of nerve growth factor was unsuccessfully used for skin ulcers

in the setting of systemic sclerosis.<sup>6</sup> We report the effects of topical rhbFGF for the treatment of ulcers in a patient with systemic sclerosis. bFGF receptors are strongly expressed on the neocapillary endothelial cells and on granulation tissue fibroblasts.<sup>2,7-11</sup> bFGF binds to these FGF receptors and induces fibroblast activation and vascular proliferation. During the wound-healing process, especially the restructuring phase, bFGF also stimulates keratinocyte proliferation.<sup>5</sup> These mechanisms may underlie the rapid reepithelialization in the present case.

Painful chronic lesions on the legs greatly impaired our patient's quality of life. Topical rhbFGF appears to be a safe and effective tool for treating ulcerative skin lesions in systemic sclerosis and related diseases.

## REFERENCES

1. Hafner J, Schneider E, Burg G, et al. Management of leg ulcers in patients with rheumatoid arthritis or systemic sclerosis: the importance of concomitant arterial and venous disease. *J Vasc Surg.* 2000;32:322-329.
2. Takenaka H, Kishimoto S, Tooyama I, et al. Protein expression of fibroblast growth factor receptor-1 in keratinocytes during wound healing in rat skin. *J Invest Dermatol.* 1997;109:108-112.
3. Youssef P, Brama T, Englert H, et al. Limited scleroderma is associated with increased prevalence of macrovascular disease. *J Rheumatol.* 1995;22:469-472.
4. Takehara K. Growth regulation of skin fibroblasts. *J Dermatol Sci.* 2000;24(suppl 1):S70-S77.
5. Kibe Y, Takenaka H, Kishimoto S. Spatial and temporal expression of basic fibroblast growth factor protein during wound healing of rat skin. *Br J Dermatol.* 2000;143:720-727.
6. Tuveri M, Generini S, Matucci-Cerinic M, et al. NGE, a useful tool in the treatment of chronic vasculitic ulcers in rheumatoid arthritis. *Lancet.* 2000;356:1739-1740.
7. Okumura M, Okuda T, Nakamura T, et al. Effect of basic fibroblast growth factor on wound healing in healing-impaired animal models. *Arzneimittelforschung.* 1996;46:547-551.
8. Friesel RE, Maciag T. Molecular mechanisms of angiogenesis: fibroblast growth factor signal transduction. *FASEB J.* 1995;9:919-925.
9. Nugent MA, Iozzo RV. Fibroblast growth factor-2. *Int J Biochem Cell Biol.* 2000;32:115-120.
10. Powers CJ, McLeskey SW, Wellstein A. Fibroblast growth factors, their receptors and signaling. *Endocr Relat Cancer.* 2000;7:165-197.
11. Takenaka H, Yasuno H, Kishimoto S. Immunolocalization of fibroblast growth factor receptors in normal and wounded human skin. *Arch Dermatol Res.* 2002;294:331-338.