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LETTER TO THE EDITOR

Novel approach to ischemic skin ulcer in systemic lupus erythematosus: Therapeutic angiogenesis by controlled-release basic fibroblast growth factor

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Dear Editor,

Systemic lupus erythematosus (SLE) frequently involves the vascular system, and the acquired inflammatory process is known to accelerate atherosclerosis. We report a 65-year-old woman with SLE complicated by an ischemic skin ulcer of the superior portion of the right lateral malleolus which was untreatable by local therapy. The ankle–brachial index was reduced to 0.72 in the right leg, and transcutaneous oxygen tension ($TcPO_2$) at the dorsum of the right foot was 1.0 mmHg (normal limit: >30 mmHg) with no increase after pure oxygen inhalation. Angiography revealed total occlusions of all the below-the-knee arteries with poor distal collateral circulation, indicating an Inter-Society Consensus type D lesion. Because the patient's SLE disease activity index was 11 points under the administration of prednisolone and methotrexate, invasive therapy by percutaneous or surgical revascularization was not preferable. Thus, we decided to perform therapeutic angiogenesis by administration of controlled-release basic fibroblast growth factor (bFGF)-incorporated biodegradable gelatin hydrogel. Four weeks after the therapy, there was no significant improvement in ankle–brachial index (ABI) and angiographic findings. Instead, basal $TcPO_2$ was increased to 10 mmHg with an additional increase up to 39 mmHg by oxygen inhalation. Furthermore, the ulcer healed completely without any complications. This result suggests that bFGF protein therapy using the drug delivery system can be a promising approach to intractable skin ulcers complicating SLE.

Systemic lupus erythematosus is manifested by an interaction between susceptible genes and environmental risk factors, which leads to autoimmune reactions. As the next step, generated autoantibodies and immune complexes deposited in tissue activate complement, induce inflammation and lead to irreversible organ damage.[1] SLE frequently involves the vascular system, and the occurring inflammation accelerates atherosclerosis. Roman *et al.* reported that the prevalence of atherosclerosis was significantly higher in patients with SLE, and the accelerated atherosclerosis was not attributable to traditional cardiovascular risk factors.[2] Furthermore, progressive ischemic skin ulcers, requiring limb amputation, occasionally complicate SLE.

Previously, we demonstrated that i.m. administration of controlled-release bFGF-incorporated biodegradable gelatin hydrogel successfully improved leg ischemia and cured a skin ulcer in a patient with Churg–Strauss syndrome.[3] In the present case, we applied this novel treatment approach to a patient with SLE complicated by an unhealed skin ulcer, and achieved successful improvement of the local skin blood perfusion and healing of the skin ulcer 4 weeks after the therapy.

A 65-year-old woman, diagnosed with SLE at 42 years old, was referred to our hospital with resting pain of her right foot complicated by a skin ulcer of the superior portion of her right lateral malleolus (Fig. 1a), which was not improved by topical and systemic medication for 1 month. As a conventional therapy for peripheral arterial disease, cilostazol and prostaglandin agents were used before admission, and

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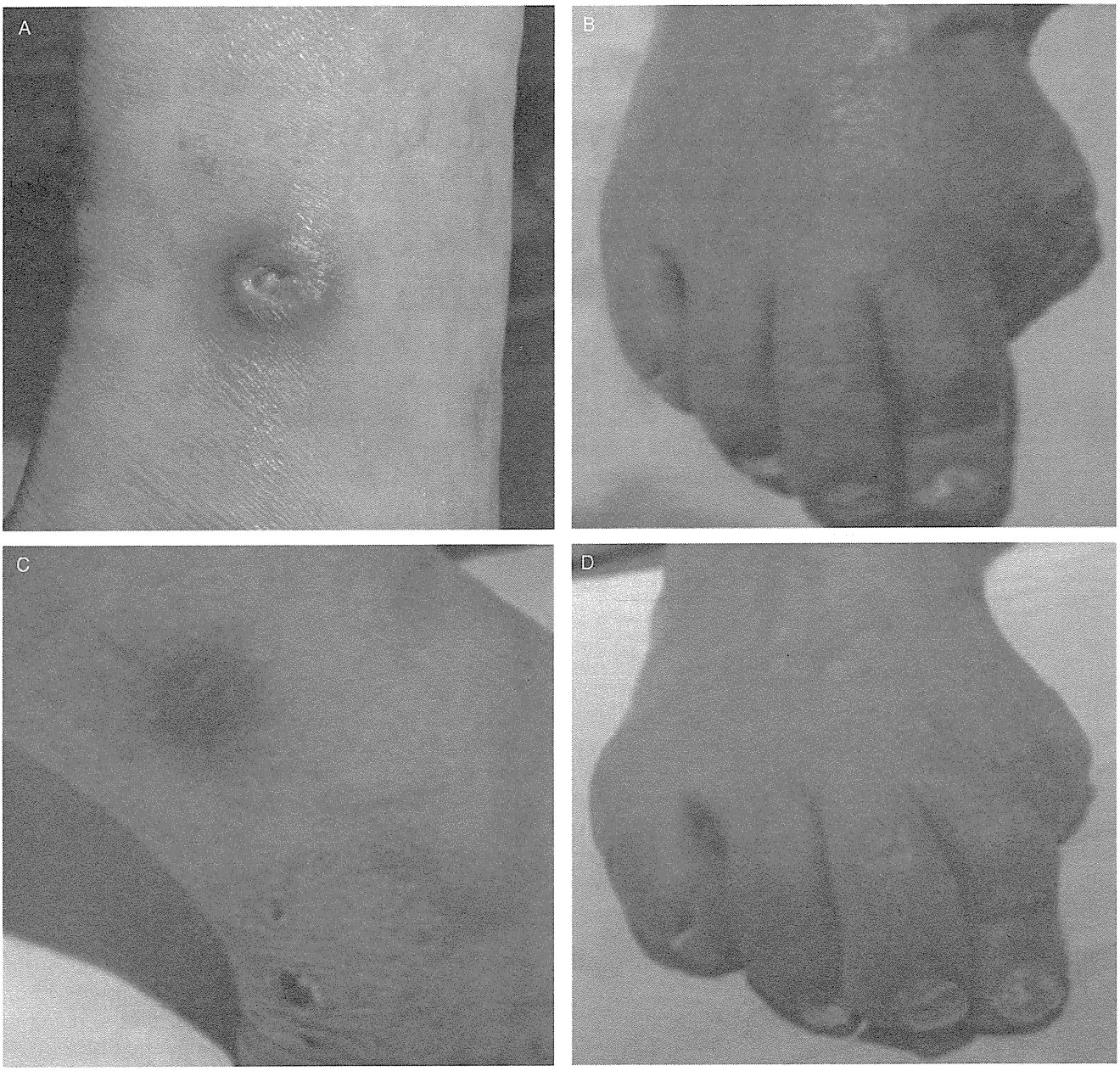

Figure 1 (a) Skin ulcer of superior portion of right lateral malleolus and (b) cyanosis of right toes and edema of dorsum of right foot before therapy. Four weeks after therapy, (c) the skin ulcer had healed completely, and (d) cyanosis and edema had improved.

that was continued through the follow-up period. She had been given prednisolone as standard treatment since 42 years of age and maintained on 5 mg until now. Cyanosis of the right toes and edema of the dorsum of the right foot were also noted (Fig. 1b). Blood examination showed elevated C-reactive protein (0.75 mg/dL), immunoglobulin G (2193 mg/dL), anti-centromere antibody (68.4 index) and anti-double-stranded DNA antibody (23 IU/mL) levels. The SLE disease activity index was 11 points, indicating an active state.[4] Angiography revealed total occlusions of the right anterior tibial artery, right posterior tibial artery and right peroneal artery, and the dorsalis pedis artery was barely supplied by collateral circulation (Fig. 2). Severe ischemia was shown by blood flow examinations, reduced ABI in the right leg (0.72), severely reduced $TcPO_2$ at the dorsum of the right foot (1.0 mmHg; normal limit: >30 mmHg) and absence of $TcPO_2$ response to pure oxygen inhalation. From this clinical profile and angiographic findings, the advisory committee (consisting of cardiologists, vascular surgeons, plastic surgeons, radiologists and anesthetists)

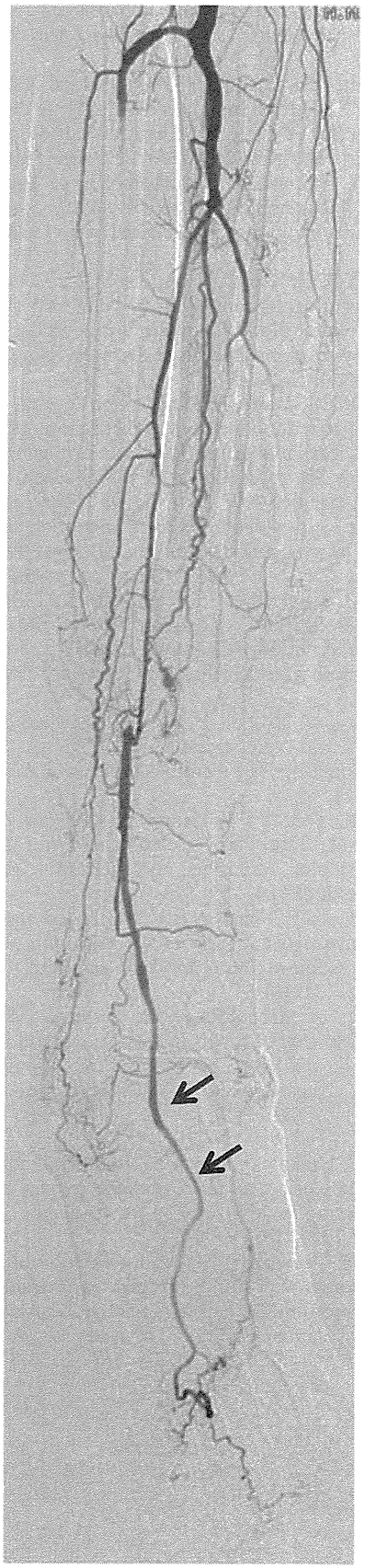

Figure 2 Digital subtraction angiography revealed total occlusions of right anterior tibial artery, right posterior tibial artery and right peroneal artery. The dorsalis pedis artery was enhanced by collateral circulation (arrow).

determined that these vascular lesions were unsuitable for percutaneous or surgical revascularization. We then decided to apply therapeutic angiogenesis by administration of controlled-release bFGF-incorporated gelatin hydrogel to improve local blood perfusion as an alternative treatment for limb salvage.

Gelatin hydrogel was prepared as previously described,[5] and impregnated with an aqueous solution containing recombinant human bFGF, followed by leaving it at 4°C for over 12 h to obtain bFGF-incorporated gelatin hydrogel. Under general anesthesia, we injected bFGF (600 μg)-incorporated gelatin hydrogel directory into the calf muscle at 20 sites around the ulcer.

Four weeks after the therapy, resting pain had disappeared, and the ulcer had healed completely (Fig. 1c). Cyanosis of the right toes and edema of the right dorsal foot were also improved (Fig. 1d). Local skin perfusion determined by $TcPO_2$ was improved (10 mmHg) and maximum $TcPO_2$ was enhanced (39 mmHg), although angiographic findings and ABI (0.66) were not changed. Dosage of prednisolone (5 mg/day) and methotrexate (2 mg/week) for SLE were not altered during the period. Serological findings reflecting SLE activity, such as serum complement level, serum albumin level and white blood cells count, and SLE disease activity index did not change after the therapy.

In cases of peripheral arterial disease associated with connective tissue diseases such as SLE, we have experienced that those patients are especially unsuitable for catheter and surgical revascularization due to pathological characteristics such as continuous inflammation of the vascular bed, and anatomical characteristics such as distal arterial obstruction. For such patients, there are some reports that therapeutic angiogenesis by implantation of autologous mononuclear cells obtained from bone marrow or peripheral blood into the ischemic lesion is effective.[6,7] On the other hand, there is a report that endothelial progenitor cell function is inhibited, especially in SLE patients treated with corticosteroids,[8] and also production of angiogenic factors from bone marrow cells is suppressed.[9,10] Thus, the effects of implantation of bone marrow mononuclear cells as therapeutic angiogenesis are inconclusive and still under debate. Here, we propose a novel protein therapy using bFGF that is simpler and less invasive than the cell transplantation.

First, we focused on a single growth factor, bFGF, which is known to play a major role in angiogenesis. This factor modulates proliferation and migration of

ndothelial cells in the early phase, and contributes to vessel maturation by matrix deposition and pericyte recruitment in the late phase.[11] Thus, bFGF is considered to be suitable for therapeutic angiogenesis.[12] Second, because bFGF plays an important role in granulation tissue formation, re-epithelialization and tissue remodeling,[13] administration of bFGF in ischemic tissue is thought to be effective in ulcer healing. Third, human recombinant bFGF is clinically available in Japan. Fourth, a drug delivery system has been utilized in order to maximally potentiate the drug effect, by means of a prolonged clinical half-life of the drug through slow and stable release.[14,15] As mentioned earlier, the therapeutic effect was confirmed in a patient with Churg–Strauss syndrome who developed an intractable leg ulcer with a similar pathogenic background to SLE.[3] Thus, we thought this therapy would be safe and effective also in this elderly patient with SLE.

In the present case, we found that $TcPO_2$ reflecting local microcirculation was increased after the therapy, whereas angiographic findings and ABI were not changed. It can be inferred that the therapeutic angiogenesis might increase regional microperfusion sufficient to heal a wound by enhancing mainly neocapillary formation rather than arteriogenesis which may result in an elevation of leg blood pressure.[16]

In summary, application of controlled-release bFGF successfully improved local skin blood flow, and eventually cured the ischemic skin ulcer in this case. Our findings suggest a novel clinical approach to ischemic skin ulcers associated with SLE.

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