

Successful treatment of infliximab in a patient with scleroderma: a case report

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Abstract

Rationale: Systemic Scleroderma (SSc) is a rare connective tissue disease clinically characterized by cutaneous sclerosis and variable systemic involvement. No drug is currently available to effectively reverse the fibrotic process in SSc. Previous reports have suggested that the tumor necrosis factor (TNF) antagonists could be useful for the treatment of fibrotic disorders. However, TNF α has long been considered as an antifibrotic cytokine. Whether TNF antagonist is effective for SSc patients needs to be tested.

Patient concerns-Diagnosis: Here we report a case with a 2-year history of SSc who was effectively treated with infliximab in our clinic.

Interventions: The patient manifested skin thickening, chest tightness and arthralgia. Before admitted to our clinic, he was treated with methylprednisolone, prostacyclin, D-penicillamine and calcium antagonists but without significant improvement of his signs and symptoms. In our clinic, the patient was treated with infliximab.

Outcomes: His signs and symptoms were continued improving during the course of treatment. His skin biopsy showed significant reduction in fibroplasia finally.

Lessons: TNF antagonist is an effective treatment for SSc.

Abbreviations: CPK = creatine phosphokinase, dcSSc = diffused cutaneous systemic scleroderma, DLco = diffusing capacity of the lungs for carbon monoxide, ESR = erythrocyte sedimentation rate, FVC = forced vital capacity, lcSSc = limited cutaneous systemic scleroderma, SSc = systemic scleroderma, TNF = tumor necrosis factor, TNFR II = tumor necrosis factor receptor II.

Keywords: scleroderma, skin biopsy, tumor necrosis factor

1. Introduction

Systemic scleroderma (SSc) is a rare connective tissue disease clinically characterized by cutaneous sclerosis and variable systemic involvement. Patients can be classified into 2 subsets based on the distribution of skin changes: diffused cutaneous SSc (dcSSc) and limited cutaneous SSc (lcSSc).^[1] It is reported that patients with dcSSc tend to have a higher risk of multisystem disease and poor prognosis.^[1] No drug is currently available to effectively reverse the fibrotic process in SSc. Tumor necrosis factor (TNF) antagonists were reported to be useful for the treatment of fibrotic disorders.^[2-7] However, TNF α has long been considered an antifibrotic cytokine.^[8-10] Whether TNF antagonist is effective for SSc patients needs to be tested. Here, we report a case with a 2-year history of dcSSc who failed to response to traditional treatments. The patient was treated with infliximab

in our clinics, and he achieved remarkable improvement in skin, joints, and myopathy during the treatment. Skin biopsy taken after fourth infusion of infliximab showed significant reduction in fibroplasia and TNF. We suggest that TNF antagonist is an effective treatment for SSc.

2. Case presentation

A 66-year-old male patient who complained of skin thickening and arthralgia was referred to our department on October 17, 2014. He began suffering from skin swelling and nonpitting edema on his trunk and legs since November 2012, and since then, the symptoms deteriorated gradually. He began complaining of muscle weakness, chest tightness, and arthralgia in both hips since 2014. The patient was diagnosed with SSc according to 2001 LeRoy and Medsger^[1] criteria and treated with methylprednisolone, prostacyclin, D-penicillamine, and calcium antagonists. However, his manifestations failed to get improving with above treatment. At admission to our clinic, his physical examination showed thickness and hyperpigmentation on his trunk and limbs. Limb examination revealed proximal weakness. The erythrocyte sedimentation rate (ESR) was 44 mm/h, and serum creatine phosphokinase (CPK) was 563 U/L. Additional laboratory findings included an antinuclear antibody titer of 1:100 dilution with a granular pattern. Tests for antibodies to extractable nuclear antigens, antiphospholipid, and β 2-glycoprotein were all negative. Pulmonary function test revealed a serious restrictive pattern, and his forced vital capacity (FVC) was less than 1 L. The patient was unable to perform diffusing capacity of the lungs for carbon monoxide (DLco) due to incapacity of holding his breath. Blood gas analysis showed a PaO $_2$ of 90 mm Hg without oxygen at rest. High-resolution computed tomography of the chest was normal. An echocardiogram indicated his

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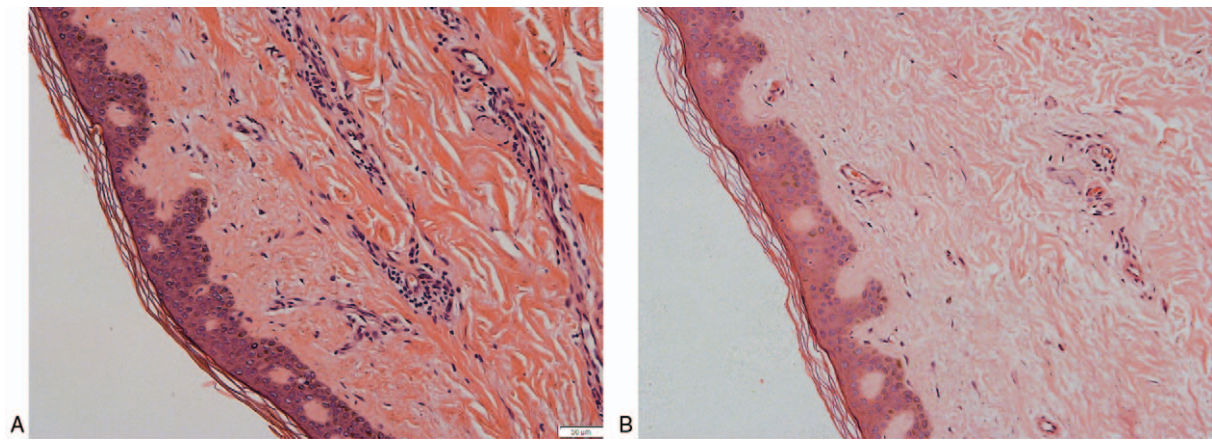


Figure 1. Hematoxylin and eosin staining of skin biopsy (original magnification $\times 200$): (A) skin biopsy taken from clinically affected abdomen demonstrated increased collagen with a few lymphocytes in the dermis, (B) skin biopsy taken after the treatment of infliximab indicated reduction in fibroplasia.

pulmonary artery systolic pressure as 26 mm Hg. Skin biopsy (4 mm^2) from the clinically affected skin of the abdomen showed increased collagen with a few lymphocytes and an elevated level of TNF in the dermis (Figs. 1A and 2A). Given his clinical condition and progression of the disease without any effective treatment, infliximab was prescribed after obtaining informed consent from the patient and getting approval from our hospital ethical committee. The first infusion containing a dose of 3 mg/kg infliximab was started on November 07, 2014 and repeated 2 and 6 weeks later, and subsequently every 8 weeks. The patient's joint symptoms were relieved substantially immediately after the first infusion, and chest tightness was significantly diminished after the second infusion. After the fifth infusion, the patient felt great improvement on skin hardening. His pulmonary function test improved with a normal FVC and CPK, and DLco/VA was 93.5%. Modified Rodnan skin score declined from 11 to 7. A biopsy specimen taken after the fourth infusion of infliximab showed significant reduction in fibroplasia and TNF compared with that taken before the infliximab treatment (Figs. 1B and 2B).

3. Discussion

SSc is a rare connective tissue disease clinically characterized by cutaneous sclerosis and variable systemic involvement. Patients can be classified into 2 subsets based on the distribution of skin changes: dcSSc and lcSSc.^[1] Our patient was considered to have dcSSc as his skin manifestations were found proximal to the elbows and knees, including the trunk and thighs. It is reported^[1] that patients with dcSSc tend to have a higher risk of multisystem disease and poor prognosis. No drug is currently available to reverse the fibrotic process in scleroderma effectively. As the patient failed to respond to traditional treatments including systemic corticosteroids, prostacyclin, and D-penicillamine, we tried infliximab based on the following observations: the patient had the clinical manifestations of joint inflammation; his ESR was 44 mm/h, indicating the possibility of an inflammatory process; skin biopsy revealed the presence of lymphocytes and elevation of TNF in the dermis; and systemic administration of corticosteroids did not work with substantial adverse effects.

Serum TNF- α levels were found to be significantly elevated in SSc patients as compared with healthy controls.^[2] TNF- α has

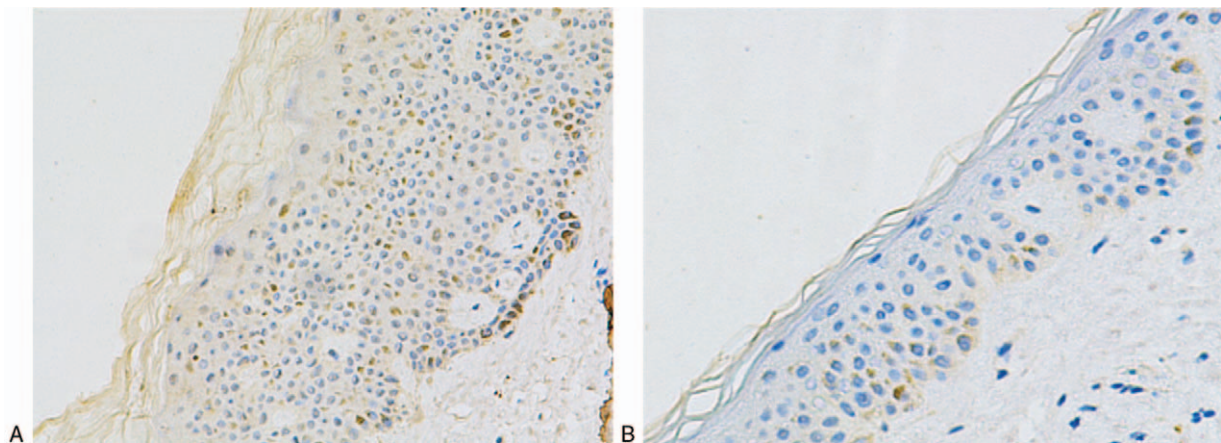


Figure 2. Immunoperoxidase stain for tumor necrosis factor (TNF) of skin biopsy (immunoperoxidase stain for TNF, original magnification $\times 200$): (A) light microscopic image of affected skin on abdomen taken before treatment with infliximab demonstrated the elevated TNF in the skin. Integrated optical density (IOD) = 4539.3, (B) light microscopic image of affected skin on abdomen taken after treatment with infliximab indicated the decreased but still elevated TNF in the skin. IOD = 1200.3.

been proved to have profibrotic effects. It was reported that TNF- α -secreting B cells were involved in myocardial fibrosis.^[3] T lymphocytes in SSc tissue were found to overexpress TNF receptor II (TNFRII), and costimulation of T cells via TNFRII further could trigger collagen production.^[4] TNF- α inhibitors could reduce systemic inflammation, improve the endothelial function, decrease the risk of pulmonary arterial hypertension progression, and prevent the occurrence of acute cardiovascular and/or cerebrovascular events.^[5] Anti-TNF treatment may also improve inflammatory arthritis and disability in SSc.^[6,7] However, the role of TNF- α in fibrotic diseases remains controversial.^[8] TNF- α was reported to downregulate the production of tissue growth factor- β 1, which in turn could stimulate extracellular matrix molecules.^[9] It has long been known that TNF α could inhibit the synthesis of type I, III collagen, and fibronectin.^[10] It was reported^[11] that T helper cell 17 cells inhibited collagen production with a mechanism partially dependent on interleukin-17, TNF, and interferon- γ . There were also studies reporting some fatal adverse events after the treatment of anti-TNF due to fibrosing alveolitis.^[12,13] Therefore, it is assumed that TNF- α may work simultaneously as a profibrotic agent and an antifibrotic agent. On one hand, TNF- α suppresses the production of collagen and stimulates the release of matrix metalloprotein. On the other hand, at the early stage of SSc, TNF- α activates inflammatory cells, which secrete profibrotic mediators and meanwhile stimulate fibroblasts.^[8] Skin biopsy in our patient revealed the presence of inflammatory infiltrates and elevation of TNF α in the dermis, indicating the profibrotic effect of TNF α in skin fibrosis via inflammatory signaling in SSc. Therefore, TNF inhibitor should be effective in certain cases of SSc like we report here.

4. Conclusion

The case reported herein demonstrated remarkable improvement in the skin, joints, and myopathy in an SSc case after the treatment with the TNF inhibitor infliximab. TNF level in skin biopsy was reduced markedly after treatment with infliximab in

our patient. According to our experience with the use of infliximab, at least 1-year treatment is required to obtain obvious therapeutic efficacy. Skin biopsy is a useful index for evaluation of the effect of anti-TNF therapy on this disease.

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