Case report

Treatment of psoriasis with ustekinumab improved skin tightening in systemic sclerosis

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ABSTRACT

Systemic sclerosis (SSc) is a chronic autoimmune disease characterised by fibrosis, inflammation and vasculopathy in the skin and internal organs. Recently, several articles described that Th17 cells, IL-23 and IL-17 levels were significantly elevated in the peripheral blood or fibrotic sites of SSc. We report a case of SSc and psoriasis administered ustekinumab, IL-12/IL-23 inhibitor. In this case, the skin tightening was successfully improved and ustekinumab was more effective, even though oral prednisolone (9-12 mg/day) had some effect on skin tightening and arthralgia. We consider that inhibition of Th17 cytokines may lead to therapeutic efficacy against SSc. Ustekinumab has the potential for a treatment option of SSc.

Introduction

Systemic sclerosis (SSc) is a chronic autoimmune disease characterised by three major clinical features: fibrosis, inflammation and vasculopathy in the skin and internal organs. Immune activation is involved in excessive deposition of extracellular matrix molecules in SSc. Especially, transforming growth factor-β (TGF-β) is considered to be a key player (1). Recently, several articles described about Th17 cytokine profiles in SSc or other autoimmune diseases (2). Th17 cells were discovered in 2007 as the third T helper cell subset that can produce IL-17A. Naïve $CD4^+$ T cells are differentiated into various subsets of helper T cells or regulatory T cells depending on the local cytokine conditions. TGF-β and inflammatory cytokines, such as IL-6, IL-21, IL-1β, and IL-23, are essential for the differentiation of Th17 cells. IL-23 is also required for Th17 cells to induce and maintain tissue inflammation by amplifying proinflammatory cytokines (3, 4). Usually, immunosuppressive therapies, such as cyclophosphamide and low-dose glucocorticoids, are selected for progressive and diffuse skin fibrosis in Japanese patients with SSc. In this report, we described a case of SSc with psoriasis successfully improved the skin tightening by ustekinumab, IL-12/IL-23 inhibitor.

Case report

A 51-year-old Japanese man presented with myalgia, muscle weakness and multiple arthralgia of his shoulders, elbows, wrists and hand joints. He also had morning stiffness of his fingers. Physical examination revealed sclerodactyly and skin tightening of his hands, forearms and face which was assessed by 10 of modified Rodnan's total skin score (mRSS), accompanying joint contractures of his hands. Finger flexions were 10 mm (right) and 11 mm (left). Raynaud's phenomenon, nail fold bleeding, telangiectasias, digital ulcers, gastro-oesophageal reflux and interstitial pneumonia were not seen. The immunology profile showed positive (fine speckled pattern) for antinuclear antibody immunofluorescence test and negative for anti-topo I antibodies, anti-centromere antibody, anti-SS-A/SS-B antibody, anti-RNP antibody, anti-neutrophil cytoplasmic antibody, anti-phospholipid antibody and anti-CCP antibodies. Laboratory blood examination including liver and renal functions, matrix metalloproteinase-3, rheumatoid factor and creatine kinase were within normal range except for elevated C-reactive protein (4.2 mg/dL) and erythrocyte sedimentation rate (33 mm/1hr). Histopathologic examination from his left dorsal forearm suggested thickening and hyalinisation of connective tissue of deep dermis. MRI scan of skeletal muscles showed no abnormal

findings. He also had scaly erythemas which were diagnosed as psoriasis vulgaris when he was 51 years old. After one year of the onset, he was diagnosed as having diffuse systemic scleroderma and polymyalgia rheumatica.

After admission, oral prednisolone (20 mg/day) started to control skin sclerosis and polymyalgia rheumatic. Two weeks after taking oral prednisolone, myalgia and C-reactive protein improved, even though he still had arthralgia, sclerodactyly and skin tightening. Oral prednisolone was gradually decreased for 5 years (12 mg/day). During the treatment of skin sclerosis, the eruption of psoriasis worsened which was scored 8.4 by PASI (Psoriasis Area and Severity Index). Because the arthralgia was still remained, we decided to start infliximab at a loading dose of 5 mg/kg/day to control psoriasis. The mRSS of his skin tightening was 4 at that point. He achieved 90% improvement of the PASI score after 5 months, however infusion rection (face flushing, wheals, itchiness and abdominal pain) occurred when the fifth infliximab was administered intravenously. Furthermore, infliximab was becoming ineffective. We withdrew infliximab and switched to ustekinumab at a standard dose of 45 mg/day when his PASI score was 5.0. At this point, the mRSS of his skin tightening remained 4. The PASI score was gradually decreased to 0.8 during 4 months of ustekinumab treatment. We continued the administration of ustekinumab, then PASI 0 was achieved in 1 year and mRSS was also gradually decreased to 0 in 2 years after initiation of ustekinumab. Both Finger flexions were improved to 0 mm. Oral prednisolone was decreased to 9 mg/day. The treatment of ustekinumab is still continued without any side effects.

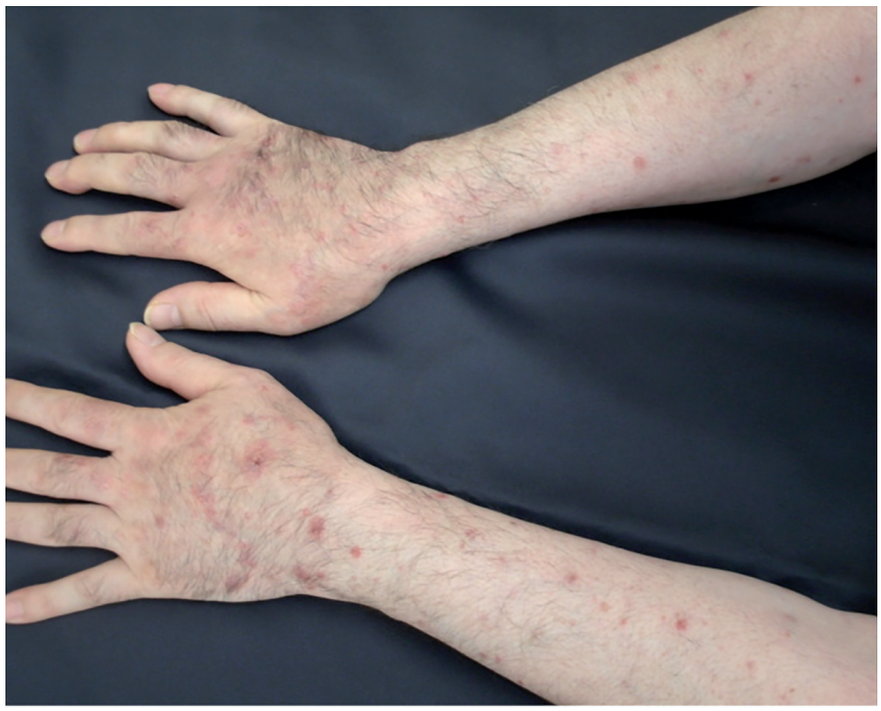

Fig. 1. Skin tightening and psoriatic eruptions of his hands and forearms.

Discussion

Here we report successful treatment of ustekinumab against not only psoriasis but also skin tightening in SSc. To our knowledge, this is the first case report of SSc whose skin tightening was improved by ustekinumab. Since 2011, ustekinumab has been approved in Japan as a new biological agent for moderate to severe psoriasis vulgaris and psoriatic arthritis. Ustekinumab is a human monoclonal antibody which inhibits p40 subunit of both IL-12 and 23. Ustekinumab contributes to the successful results in the treatment of psoriasis in Japan. Furthermore, ustekinumab has also been applied for the approval for Crohn's disease recently.

For the last decade, it is well recognised that the IL-23/Th-17 axis plays an important role in the pathogenesis of psoriasis. IL-23/Th-17 axis is also related to other inflammatory autoimmune disorders, for example, systemic sclerosis, multiple sclerosis, inflammatory bowel disease, and rheumatoid arthritis. Previous reports described that Th17 cells, IL-23 and IL-17 levels were significantly elevated in the peripheral blood or fibrotic sites of SSc. (5-7) Serum IL-23 levels were reported to be increased especially in early stages of the disease and have correlations with the disease duration and the prevalence of pulmonary fibrosis (6). IL-23 has been reported to be involved in the pathogenesis of SSc including the secretion of pro-inflammatory cytokines, the recruitment of monocytes and the triggering of granulocyte-macrophage colony-stimulating factor (8). Recent studies demonstrated that Th17 cells and cytokines contribute to not only inflammation but also skin and lung fibrosis by enhancing fibroblast proliferation and cytokine production in a mouse model of SSc (9, 10). In our case, oral prednisolone was used (9-12 mg/day) in addition to infliximab or ustekinumab. Considering that skin tightening and arthralgia disappeared after administration of ustekinumab, ustekinumab was more effective in this case, even though oral prednisolone had some effect on skin tightening. There are some molecular therapeutic candidates against fibrosis of systemic sclerosis including TGFβ, VEGF, PDGF and c-Kit (11). Recent studies and this case report show that Th17 cytokines also can be the therapeutic target of systemic sclerosis.

In summary, inhibition of Th17 associated cytokines may lead to therapeutic efficacy against SSc. Ustekinumab has the potential for a treatment option of SSc.

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