http://dx.doi.org/10.5021/ad.2014.26.6.766

Skin Sclerosis with Elevation of Serum Interleukin-6 That Is Possibly Associated with Immunoglobulin 4-Related Disease

Sei-ichiro Motegi, Akihiko Uchiyama, Kazuya Yamada, Akihito Uehara, Sayaka Toki, Osamu Ishikawa

Department of Dermatology, Gunma University Graduate School of Medicine, Gunma, Japan

Dear Editor:

An 82-year-old Japanese man was found to have retroperitoneal fibrosis in 2006 and treated with 60 mg/day prednisolone, which tapered and finally discontinued in January 2010. Arthritis of both knees developed in 2011, and total knee arthroplasty was performed in January 2013. Histopathological examination of the joint synovium showed numerous infiltrations of plasma cells and fibrosis around the infiltrate (Fig. 1A). The ratio of immunoglobulin $G4^+$ ($IgG4^+$)/IgG^+ plasma cells per high-power field was $>60\%$ (Fig. 1B). Serum IgG4 was elevated (125 mg/dl; reference, 4～108 mg/dl). IgG4-related disease (IgG4-RD) with involvement of the retroperitoneum and joint synovium was established. Computed tomography showed the remaining lesion of retroperitoneal fibrosis but did not show additional lesions of IgG4-RD. One month after the operation, he noticed an indurated skin lesion in his lower leg. Physical examination revealed diffuse, indurated skin sclerosis in his left lower leg (Fig. 1C). Histological examination revealed severe fibrosis in entire dermis and infiltrations of plasma cells around blood vessels (Fig. 1D). $IgG4^+$ cells were rarely observed. Skin sclerosis appeared sequentially after the operation on the joint synovium and the establishment of the diagnosis of IgG4-RD, suggesting that skin sclerosis may be considered as the possible symptom of IgG4-RD. Topical and oral prednisolone (15 mg/day) was given. The skin sclerosis became soft gradually, and serum IgG4 levels returned to the reference range. We also found that the serum interleukin (IL)-6 level was elevated (13 pg/ml; reference, <0.5) before treatment and returned to the reference range in parallel with clinical improvement.

IgG4-RD is a newly recognized disorder characterized by the infiltration of abundant $IgG4^+$ plasma cells in lesions accompanied by fibrotic or sclerotic changes[1,2]. Skin involvement was rarely reported[1]. Ikeda et al.[1] described the skin lesions as erythematous nodules, papules, and areas of induration. They also reported that the common feature of the skin lesions was the localization near the main area of IgG4-RD involvement, and that the appearance of skin lesions after the onset of IgG4-RD range from 2 months to 3 years[1]. Of note, our case is consistent with these features.

Recently, there has been a report on 3 patients who had skin lesions with abundant infiltration of IgG4-bearing plasma cells and an elevated serum IL-6[2]. An increase in IL-6 concentration has also been reported in other plasma cell-related diseases, including multicentric Castleman's disease and cutaneous plasmacytosis[3]. IL-6 induces B-cell proliferation and terminal differentiation, immunoglobulin secretion, and an acute inflammatory-phase response, suggesting that IL-6 might be important in the pathogenesis of IgG4-RD.

Concerning IL-6 and fibrosis, it has been reported that serum IL-6 correlated with the extent of skin fibrosis in systemic sclerosis[4]. In addition, IL-6 enhanced collagen type I production from human fibroblasts in an *in vitro* assay[5],

Received October 22, 2013, Revised November 13, 2013, Accepted for publication November 17, 2013

Corresponding author: Sei-ichiro Motegi, Department of Dermatology, Gunma University Graduate School of Medicine, 3-39-22 Showa-machi, Maebashi, Gunma 371-8511, Japan. Tel: 81-27-220-8284, Fax: 81-27-220-8285, E-mail: smotegi@gunma-u.ac.jp

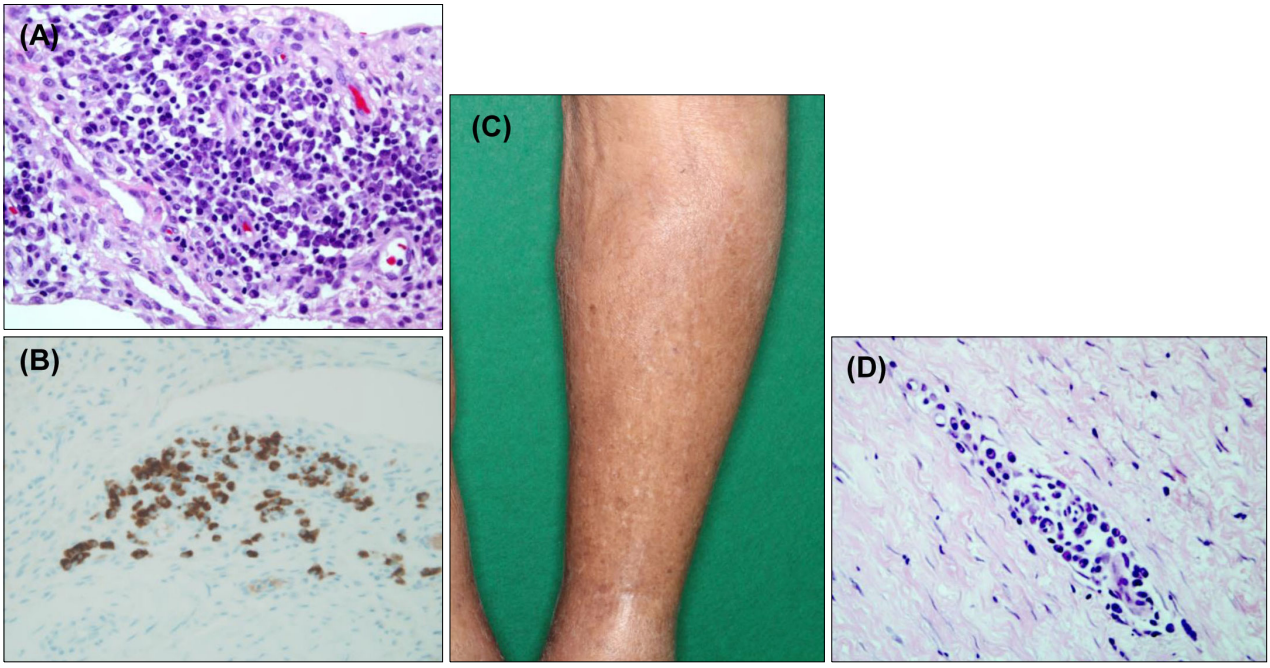

Fig. 1. (A) Histopathological examination of the joint synovium. Infiltration of plasma cells and fibrosis (H&E, ×400). (B) Infiltration of $IgG4^+$ plasma cells (×400). (C) Physical examination of the lower leg. Diffuse, indurated skin sclerosis in the left lower leg. (D) Histological examination of skin sclerosis. Severe fibrosis in the entire dermis and infiltrations of plasma cells around blood vessels were observed (H&E, ×400).

suggesting that IL-6 is a potent stimulator of collagen production in fibroblasts, leading to skin sclerosis. Thus, the elevation of serum IL-6 level might be associated with the pathogenesis of skin sclerosis in our case. However, further examinations on the relation between IL-6 in IgG4-RD and fibrosis are warranted.

REFERENCES

1. Ikeda T, Oka M, Shimizu H, Hatakeyama M, Kanki H, Kunisada M, et al. IgG4-related skin manifestations in patients with IgG4-related disease. Eur J Dermatol 2013;23:241-245.
2. Miyagawa-Hayashino A, Matsumura Y, Kawakami F, Asada H, Tanioka M, Yoshizawa A, et al. High ratio of IgG4-positive plasma cell infiltration in cutaneous plasmacytosis--is this a cutaneous manifestation of IgG4-related disease? Hum Pathol 2009;40:1269-1277.
3. Yamamoto T, Soejima K, Katayama I, Nishioka K. Intralesional steroid-therapy-induced reduction of plasma interleukin-6 and improvement of cutaneous plasmacytosis. Dermatology 1995; 190:242-244.
4. Sato S, Hasegawa M, Takehara K. Serum levels of interleukin-6 and interleukin-10 correlate with total skin thickness score in patients with systemic sclerosis. J Dermatol Sci 2001;27: 140-146.
5. Khan K, Xu S, Nihtyanova S, Derrett-Smith E, Abraham D, Denton CP, et al. Clinical and pathological significance of interleukin 6 overexpression in systemic sclerosis. Ann Rheum Dis 2012;71:1235-1242.