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A case of systemic lupus erythematosus/systemic sclerosis overlap syndrome successfully treated with belimumab

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Editor

The pathogenesis of systemic lupus erythematosus (SLE) involves various immune pathways including B cells, innate immunity and T cells [1]. Successful treatments for SLE overlap syndromes are rarely reported [2,3]. It is considered crucial to accumulate SLE overlap syndrome cases successfully treated with belimumab. Here we report a case of SLE/systemic sclerosis (SSc) overlap syndrome who showed long-term, sufficient response to belimumab.

The patient is a 31-year-old Japanese female with SLE/SSc overlap syndrome. She was diagnosed with SLE at age 18 from joint pain, high fever, stomatitis, anemia, high serum IgG, serum anti-double stranded (ds) DNA and anti-Sm antibodies, and had been treated with prednisolone (PSL) at 5 mg/day and azathioprine (AZA) at 50-100 mg/day. In her twenties, she was diagnosed with SSc based on serum anti-Scl70 antibody results and on skin sclerosis of the forearms with fingertip ulcers (*Figure 1A, B*). Mild interstitial lung disease (ILD) was also diagnosed. At age 29, bosentan was introduced for refractory fingertip ulcers (*Figure 1A, B*). At the same age, she was hospitalized twice for SLE relapses. At age 30, she was rehospitalized with fever lasting one month, weight loss, and anemia. Her ILD was stable *(Figure 1C)*. PSL was increased from 7.5 mg to 30 mg (0.75

mg/kg). Mycophenolate mofetil (MMF) was administrated, but due to pancytopenia, it was replaced by hydroxychloroquine (HCQ) 200 mg (*Figure 1D*). During the tapering of oral PSL at 5 mg/day, she had a fever over 38 ℃ and 3-kg weight loss in one month, and the blood examination results were WBC, 4100 /μl; hemoglobin (Hb), 9.9 g/dl; platelets, 289,000 μl; CRP, 0.96 mg/dl; ESR, 86 mm; C3, 106.8 mg/dl; C4, 17.6 mg/dl; anti-dsDNA antibody, 41.5 IU/ml; anti-SS-A antibody, >240 index; anti-SS-B antibody, >240 index; anti-RNP antibody, >240 U/ml; anti-Scl-70 antibody, >850 U/ml. The oral PSL was increased to 20 mg/day, and 500 mg/day of MMF was added. Two months later, we started monthly intravenous belimumab (10 mg/kg). We reduced her oral PSL rapidly from 20 mg to 5 mg without relapse. Anti-dsDNA was reduced to 15.8 IU/ml. Her SLE/SSc overlap syndrome has been well controlled for more than 2 years with PSL 5mg/day, HCQ, and belimumab.

In the Study of Belimumab in Subjects with SLE (BLISS) trials, the responders among SLE patients showed reductions in Safety of Estrogens in Lupus Erythematosus National Assessment SLE Disease Activity Index (SELENA-SLEDAI) [4], British Isles Lupus Assessment Group (BILAG) [5] score and corticosteroid dose, and lower risk of flare-ups after belimumab administration [6]. In the present case, maximum SELENA-

SLEDAI decreased (17 points to 1 point), and cumulative PSL doses over 52 weeks decreased (3,164 mg to 2,686 mg), confirming the therapeutic effect of belimumab at one year after introduction. Responders in BLISS trials were more likely to have elevated anti-dsDNA titers and low C3 or C4 levels, and to receive a corticosteroid dose >7.5 mg/day, but not immunosuppressants [6]. Our case had only elevated anti-dsDNA titers in factors predictive of good responses. The median percentage reduction of anti-dsDNA IgG was more than 2-fold greater than reduction of overall IgG in BLISS trials, and the authors noted that the effects of belimumab might be disproportionately greater on autoantibody-producing cells than on non-autoantibody-producing cells [7]. Since various autoantibodies were positive in our case, it is presumed that B cells were strongly involved in the disease development. Multiple autoantibodies coexist in overlap syndromes [3], and B cells seem to play important roles in the pathogenesis.

In studies on belimumab treatment for early SSc, the patients showed improved thickness of collagen fiber bundles and dermal thickness [8]. Rituximab-treated patients showed improvements in skin fibrosis and the prevention of lung fibrosis exacerbation [9]. From these studies, B-cell target therapies seems effective for SSc patients with local active inflammation, such as cutaneous LE/localized scleroderma overlap cases [10]. Since our

case had a long history of scleroderma, the skin sclerosis was already fixed at the time of administration, and no apparent improvements to skin symptoms, including the digital ulcers, were observed, nor were improvements to the ILD observed. Although there are few reports of treatments, such as rituximab, targeting B lymphocytes for overlap syndrome, they are likely to be effective, so further case accumulation is desired.

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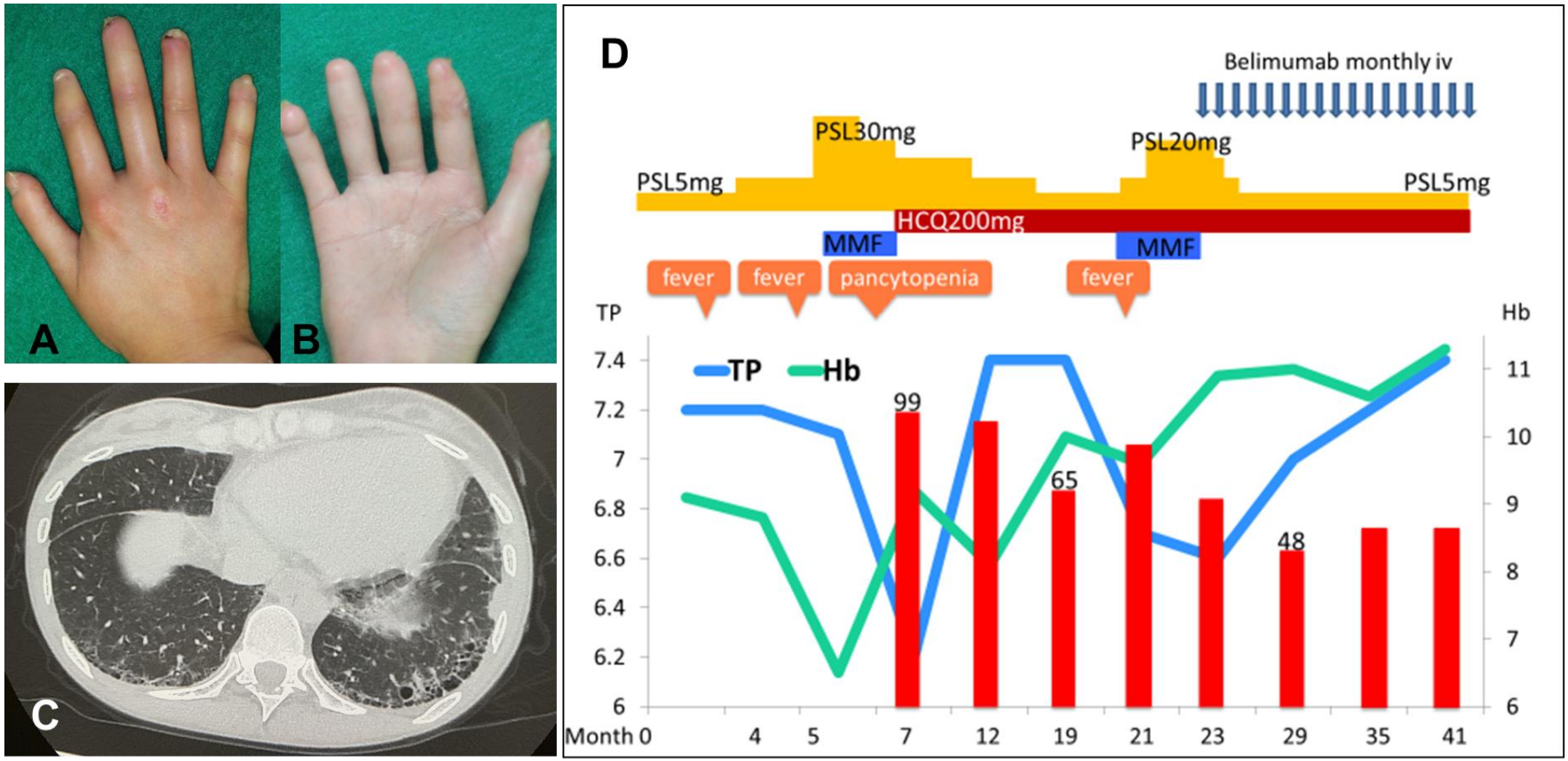
Figure 1. Skin manifestations, interstitial lung disease, treatments and disease course for the present patient.



A, B. Sclerodactyly with digital ulcers. **C.** Reticular shadow and mild bronchodilation are found in both lower lung fields. **D.** In the graph, the left vertical axis shows serum total protein (TP), and the right vertical axis shows Hb. The red bar graph shows ESR. When fever or pancytopenia occurred, both TP and Hb decreased probably due to chronic inflammation, as neither hemorrhage nor proteinuria was found. After the introduction of monthly intravenous belimumab, TP and Hb tended to increase continuously, and we noticed a marked decrease in ESR.