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Case Report

Patient with Systemic Lupus Erythematosus Combined with Erosive Arthritis was Treated Successfully with Tocilizumab: A Case Report

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Systemic lupus erythematosus (SLE) is a systemic autoimmune inflammatory disease that frequently involves the joints at some stage during the disease course. Although lupus arthritis is usually non-erosive, approximately 5% of patients develop erosions. This paper reports a patient with SLE combined with erosive arthritis, who was treated successfully with tocilizumab. A 20-year-old female, who was first diagnosed with SLE at the age of 13 years, had been admitted frequently to hospital with disease flare-ups during the previous 3 years. Despite aggressive treatment, her arthritis became aggravated, particularly in both wrists and the right knee. Radiologically, erosive arthritis was noted in the wrists.The serum interleukin (IL)-6 level was elevated significantly along with the other inflammatory markers. After the tocilizumab treatment, the arthritis subsided with a normalization of the IL-6 level, suggesting that tocilizumab may be a suitable treatment for lupus erosive arthritis if the IL-6 level is high.
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Key Words. Systemic lupus erythematosus, Arthritis, Interleukin-6 inhibitor, Interleukin-6

INTRODUCTION

Systemic lupus erythematosus (SLE) is a systemic autoimmune inflammatory disease that frequently involves the joints, which are affected in about 90% of patients at some stage of disease [1,2]. Lupus arthritis does not induce severe bone damage or erosion, unlike rheumatoid arthritis (RA). However, about 5% of patients with lupus arthritis exhibit erosions, rendering the boundary between SLE and RA obscure [2]. This apparent clinical co-existence of RA and SLE has been termed “rhupus” [3].

Recently, serological markers including interleukin-6 (IL-6), C-reactive protein (CRP), and anti-citrullinated (anti-CCP) antibody have been evaluated as predictors of joint erosion in SLE [4]. IL-6 is a pleiotropic cytokine involved in various cellular activities including inflammation, the immune response, and B-cell differentiation. Several studies have suggested that IL-6 may play an important role in SLE, inducing tissue damage [5-7]. Serum IL-6 levels were elevated in lupus patients and correlated with the extent of disease activity. B-cells from lupus patients spontaneously produce large amounts of immunoglobulins; IL-6 neutralization reduces such production [7]. Also, blocking of IL-6 inhibited the production of anti-double-stranded DNA (dsDNA) antibody in vitro [6].

Tocilizumab, a humanized IL-6 receptor-inhibiting monoclonal antibody, was first approved by the Food and Drug Administration in 2010 as a treatment for RA. As no biological agent other than belimumab has been licensed as an SLE treatment, tocilizumab has been tested in certain SLE patients, especially those who failed standard therapy. Herein, we report a case of successful use of tocilizumab to treat a patient with lupus erosive arthritis that progressed despite aggressive treatment. Consent, for the publication of the case report and any additional related

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information was taken from the patient involved in the study.

CASE REPORT

A 20-year-old female was first diagnosed with SLE at the age of 13 years when she presented with a malar rash, a vasculitic skin rash of the hand, leukopenia, a positive antinuclear antibody (>1:2,560, speckled type), a positive anti-dsDNA antibody (30.9 IU/mL), and hypocomplementemia (C3: 54 mg/dL, C4: 7 mg/dL). The tests for rheumatoid factor and anti-CCP antibody were negative. She has been admitted to hospital with flare-ups six times during recent 3 years; the problems included fever, arthritis, and lymphadenopathy, despite aggressive therapy including hydroxychloroquine (300 mg/day), moderate levels of prednisolone (20~30 mg/day), and methotrexate (10 mg/week). Lately, her arthritis had become aggravated, especially in both wrists and the right knee. We prescribed oral methotrexate (10 mg/week) and tacrolimus (2 mg/day) for 3 months, but the arthritis continued to worsen, now accompanied with fever. Magnetic resonance imaging of the right knee revealed an osteonecrotic area surrounded by a rim of low signal intensity, presumably reflecting the long-term corticosteroid treatment (Figure 1A). On hand radiography, joint space narrowing with erosion was apparent, and juxta-articular osteoporosis was also evident, similar to that associated with RA (Figure 1B). These pathologies were particularly obvious between the trapezoid, capitate, and hamate; and the second, third, and fourth metacarpal bases of the left hand. The erythrocyte sedimentation rate (ESR) was elevated to 57 mm/hour, the CRP level to 7.7 mg/dL, the C3 level to 125 mg/dL, and the C4 level to 34 mg/dL, indicating

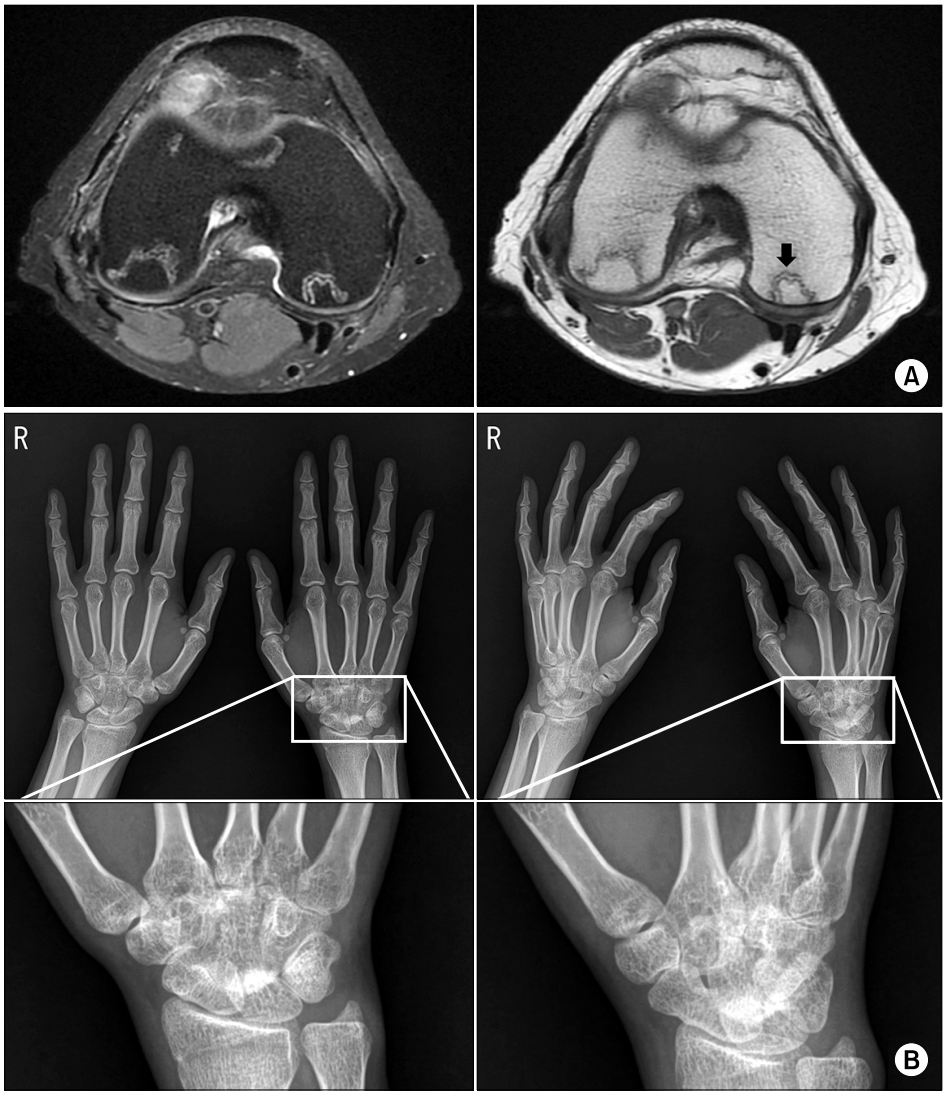

Figure 1. (A) Axial T2-weighted fat-suppressed and T1-weighted images reveal osteonecrosis with the double-line sign, representing the outer rim of the sclerosis (arrow) and the inner rim of the high-signal intensity region in the distal femoral condyles. (B) Both anteroposterior and oblique images of the left hand reveal erosion with narrowing of the joint space, and ankylosis between the trapezoid, capitate, and hamate; and the second, third, and fourth metacarpal bases.

that active inflammation was in play. The IL-6 level was significantly elevated to 106.7 pg/mL (reference range, 0～7 pg/mL). SLE disease activity index (SLEDAI) was 7, and disease activity score for 28 joints (DAS28) was 5.7. With intravenous tocilizumab treatment (400 mg/month), the fever and arthritis subsided. The ESR and CRP levels decreased to within the normal ranges, and the C3 and C4 levels fell to 56 mg/dL and 5 mg/dL (30 and 10% of their peak levels, respectively). Six months later, the IL-6 level had decreased to 59.5 pg/mL (Figure 2) with monthly intravenous tocilizumab treatment. The corticosteroid dose was reduced to 8 mg methylprednisolone daily and tacrolimus was discontinued. After discharge, the oral corticosteroid was gradually tapered, and ultimately discontinued, over a period of 2 months, but then restarted 2 months later because of relapse of the malar rash. The average disease activity score of 28 joints decreased from 5.78 to 0.6 after 10 months of tocilizumab treatment. At recent (18-month) follow-up, the arthritis was well controlled; the counts of swollen and tender joints were both zero. No manifestation of active lupus except for the malar rash developed during the period of monthly tocilizumab treatment. SLEDAI was 4, and DAS28 was 0.8. Currently, her medication includes tocilizumab (400 mg/month), methotrexate (10 mg/week), hydroxychloroquine (200 mg/day), and methylprednisolone (3 mg/day).

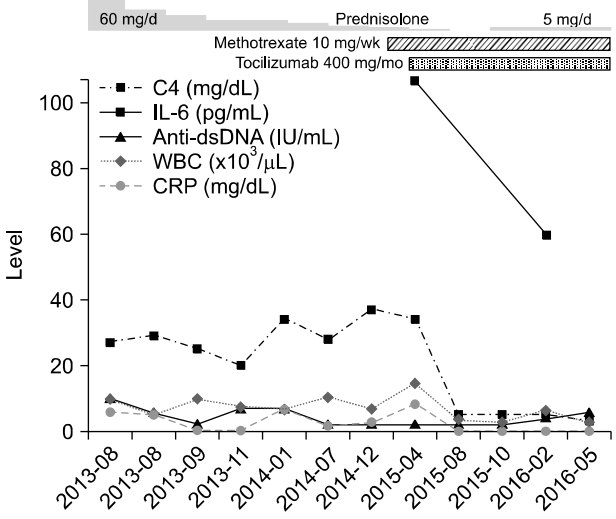

Figure 2. The time courses of the levels of complement 4 (C4), interleukin-6 (IL-6), anti-double-stranded DNA (anti-dsDNA) antibodies, white blood cells (WBCs), and C-reactive protein (CRP).

DISCUSSION

SLE is an autoimmune disease associated with diverse clinical and serological findings. The joints are commonly involved; both the small- and medium-sized joints are symmetrically affected at the time of disease onset. Although SLE may be initially confused with RA, lupus arthritis is usually well controlled with low-dose corticosteroids and antimalarial drugs. In late stages of the disease, however, the joints may develop reducible non-erosive changes termed "Jaccoud's arthritis". Unlike RA, deforming arthropathy associated with SLE is usually attributable to ligamentous rather than erosive change [8]. Efforts have been made to explain the lack of erosion in SLE arthritis compared to RA. Upregulation of interferon-inducible genes and downregulation of genes involved in extracellular matrix homeostasis have been reported in patients with SLE arthritis [9]. However, up to 3%～5% of examples of SLE arthritis are erosive, and such patients may meet the American College of Rheumatology (ACR) criteria for RA also [3]. Whether this reflects true disease overlap or, rather, the existence of a rare subtype of SLE arthritis, remains unclear. Recently, accumulating evidence has suggested that 'rhupus' reflects an overlap between RA and SLE. Budhram et al. [10] suggested that SLE-associated erosions alone do not reflect a true overlap between SLE and RA, but any additional commonality, such as elevated levels of anti-CCP antibody (a well-known marker of RA), may indicate co-existence of the two diseases.

IL-6 may play an important role in SLE, including the arthritis. One study found that plasma IL-6 levels were higher in lupus patients with than without arthritis, and correlated with both clinical and ultrasound measures of arthritis activity [11]. Joint erosion in SLE patients correlated with higher levels of IL-6 and CRP. Tocilizumab reduced SLE disease activity attributable to arthritis, suggesting that IL-6 blockade may be useful when treating drug-resistant lupus arthritis [12]. Some case reports have described SLE patients with cutaneous symptoms, hemolytic anemia or pericardial effusions intractable to standard therapy but that responded to tocilizumab [13-15]. However, any effect of tocilizumab on erosive arthritis remains unclear. Here, we report successful tocilizumab treatment of a patient with SLE combined with erosive arthritis. She did not respond to standard therapies including hydroxychloroquine, prednisolone, methotrexate, and tacrolimus. Moreover, continuous steroid

usage had triggered avascular necrosis of the right knee. After tocilizumab treatment, disease activity (including the arthritic component) became well controlled and the prednisolone dose could be reduced. Also, the levels of complement acute phase reactants were elevated before tocilizumab treatment, perhaps associated with the rise in IL-6 and CRP [16]. After tocilizumab infusion, the complement levels decreased to C3 56 mg/dL and C4 5 mg/dL, similar to those of other lupus patients and initial her manifestations of SLE including malar rash, suggesting that elevated IL-6 levels may mask hypocomplementemia in SLE patients. The reported side-effects of tocilizumab (neutropenia, liver enzyme abnormalities, alterations in lipid metabolism, and infection) were not noted in our patient [12].

SUMMARY

To the best of our knowledge, this is the first report of the successful use of tocilizumab to treat erosive arthritis in a patient with SLE. The case suggests that tocilizumab could be a treatment of choice for lupus erosive arthritis if the IL-6 level is high.

CONFLICT OF INTEREST

No potential conflict of interest relevant to this article was reported.

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