A Case of Sepsis Caused by Cellulitis in a Patient with Rheumatoid Arthritis after Tocilizumab Treatment

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Tocilizumab, a humanized monoclonal antibody against the interleukin-6 receptor, is therapeutically effective in patients diagnosed with rheumatoid arthritis (RA) compared with placebo. However patients treated with tocilizumab are at increased risk of several adverse effects including anaphylaxis and serious infections that may lead to hospitalization or death. Therefore, the risks and benefits of treatment with tocilizumab should be considered carefully and close monitoring of patients for development of signs and symptoms of side effects is required during and after treatment. Here, we report on a rare case of anaphylaxis and severe sepsis caused by cellulitis in a patient with RA after tocilizumab treatment. (J Rheum Dis 2016;23:55-60)

Key Words. Tocilizumab, Anaphylaxis, Cellulitis, Sepsis

INTRODUCTION

The recent development of biological agents has brought about many changes in the treatment of rheumatoid arthritis (RA). Despite the positive effects of the new biological agents on the treatment for patients with RA in clinical settings, they are reportedly more likely to cause adverse effects such as serious infections than the existing classical disease-modifying antirheumatic drugs (DMARDs). In particular, a strong correlation was confirmed between biological agents and increased tuberculosis infection and infections by Streptococcus pneumoniae and Listeria monocytogenes [1]. In addition, a tumor necrosis factor (TNF) inhibitor has been reported to increase the risk of musculoscutaneous infection [2,3]. However, in Korea, cellulitis has not been reported to develop after treatment with tocilizumab, a biological agent. We encountered a patient with RA who was treated with tocilizumab and experienced anaphylaxis accompanied by cellulitis in both the lower limbs and secondary sepsis. We hereby report this case along with a literature review.

CASE REPORT

A 57-year-old man was admitted to our hospital with complains of edema, ecchymosis in the lower limbs and blisters on the left dorsal foot. Nine years ago he visited with a chief complaint of pain and edema that had persisted for more than 3 months in the right elbow and the proximal interphalangeal joints of fingers on both hands. He was diagnosed with RA based on the following findings: anti-cyclic citrullinated peptide antibody ≥ 100 IU/mL; increased rheumatoid factor level (186.6 IU/mL), erythrocyte sedimentation rate (ESR; 38 mm/h), and C-reactive protein (CRP) level (2.81 mg/dL); and evidence of bone erosion in both elbows on radiography. Since then, oral methotrexate (MTX; 12.5 mg/wk) and oral methylprednisolone (2 mg/d) had been continuously prescribed. However, his symptoms did not improve with medication from 24 months prior to admission, so tacrolimus (2 mg/d) was prescribed for oral administration. However, his symptoms worsened again and the disease activity score in 28 joints increased to 5.24. Thus, intravenous administration of tocilizumab was planned be-
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cause of persisting symptoms despite treatment with more than two types of DMARDs including MTX. Prior to the commencement of treatment, he did not receive other medications, including oriental medicine, and he had no history of fish and shellfish intake or travel. He was diagnosed with tuberculosis 40 years prior and was cured after treatment and he had histories of social drinking and 40 years of smoking. He had no history of allergic disease or drug hypersensitivity reactions.

Four weeks before admission, 480 mg of tocilizumab was first administered by intravenous injection after confirmation of the negative result of intradermal skin test. Thirty minutes after the injection, the patient complained of mild generalized rash and itchiness but did not complain of edema or dyspnea, and his vital signs were normal. His symptoms improved with administration of antihistamine by intravenous injection, so he was discharged after the tocilizumab injection. When he visited the hospital for the second round of treatment with tocilizumab, an antihistamine was administered by intravenous injection prior to the intravenous administration of tocilizumab (480 mg). However, the patient developed generalized rash and itchiness that were more severe than before. He complained of dyspnea and generalized edema over the face, neck, and limbs, which was considered as anaphylaxis. Vital signs, including oxygen saturation level, were normal, and intravenous administration of tocilizumab was immediately discontinued. Antihistamine and methylprednisolone were administered by intravenous injection and thereafter, the itchiness and dyspnea improved but the generalized rash and edema persisted. The edema in both lower limbs was particularly severe, confirmed as a 2+ pitting edema on physical examination. Four days later, ecchymosis and blisters developed in the lower limbs and on the left dorsal foot, respectively.

At admission, the initial vital signs may be summarized as follows: body temperature, 37.6°C; pulse rate, 98 beats/min; blood pressure, 140/80 mmHg; and respiratory rate, 22 breaths/min. Edema was accompanied by pain, hot flushes, redness, and petechia in the lower limbs, and 4×4-cm hemorrhagic blisters were observed on the left dorsal foot (Figure 1). The peripheral blood smear showed the following values: leukocyte count, 16,950/mm³; hemoglobin level, 13 g/dL; and platelet count, 41,000/mm³. The blood chemistry values were as follows: sodium, 132 mMol/L; potassium, 3.3 mMol/L; chloride, 101 mMol/L; total protein, 5.7 g/dL; albumin, 2.5 g/dL; aspartate aminotransferase, 64 U/L; alanine aminotransferase, 15 U/L; alkaline phosphatase, 154 U/L; total-bilirubin, 1.7 mg/dL; direct-bilirubin, 0.6 mg/dL; gamma-glutamyl transferase, 30 mg/dL; prothrombin time, 13.7 s; international normalized ratio, 1.29; ESR, 32 mm/h; and CRP, 4.84 mg/dL. The urinalysis results were normal. A virus antibody test was performed again after admission, revealing HBs Ag (−), HBs Ab (−), HCV Ab (−), and AFP 14.1 ng/mL. Abdominal ultrasonography revealed mild liver cirrhosis.

Figure 1. Four days after the second intravenous administration of tocilizumab, edema and ecchymosis developed in the both lower limbs (A) and hemorrhagic blisters developed on the left dorsal foot (B).
and splenomegaly but no signs of active hepatitis. In magnetic resonance imaging (MRI) performed for both lower limbs, subcutaneous thickening with fluid collections was revealed on T2-weighted images and subcutaneous tissue and superficial fascia showed contrast enhancement. Additional involvement of deep fasciae with fluid collections, thickening, and enhancement after contrast administration were not seen. MRI confirmed cellulitis but no indication of necrotizing fasciitis (Figure 2).

After a lesion culture was performed, an empirical antibiotic therapy was commenced to treat the cellulitis. Ceftazidime, levofloxacin, and doxycycline were prescribed because a possibility of cellulitis caused by *Vibrio vulnificus* could not be excluded. Tocilizumab, methylprednisolone, and MTX were discontinued. On a blister lesion culture performed on the ninth day of admission, *Aeromonas veronii* biovar *sobria* was identified. Thus, doxycycline was discontinued and ceftazidime and levofloxacin were maintained. Bacteria were not detected in the blood and urine cultures. On the 14th day of admission, hemorrhagic blisters on the left dorsal foot burst and a 7×7-cm ulcer developed (Figure 3). In addition, abscesses developed over the entire left calf; thus, the antibiotics were switched to piperacillin/tazobactam and levofloxacin. On the 15th day of admission, the patient complained of dyspnea and lethargy. Body temperature was 38°C; pulse rate was 96 beats/min; blood pressure was 90/60 mmHg; and respiratory rate was 18 breaths/min. Rales and wheezing were heard on auscultation. The peripheral blood smear confirmed the following values: leukocyte count, 15,620/mm³; hemoglobin level, 11.1 g/dL; and platelet count, 145,000/mm³. An arterial blood test confirmed pH 7.46; PCO₂ 32 mmHg; PO₂ 57 mmHg; and SaO₂, 91%. Chest radiography findings indicated pulmonary edema. Thus, severe sepsis was diagnosed. On the 17th day of admission, debridement was performed on the ulcers on the left dorsal

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**Figure 2.** (A) Axial T2-weighted magnetic resonance (MR), left lower leg. (B) Axial T1-weighted MR, left lower leg. (C) Axial T1-weighted post contrast MR, left lower leg. (D) Axial T2-weighted MR, left lower leg. (E) Axial T1-weighted MR, right lower leg. (F) Axial T1-weighted post contrast MR, right lower leg. Subcutaneous thickening with fluid collections (arrows) was revealed on T2-weighted images and subcutaneous tissue and superficial fascia (arrowheads) showed contrast enhancement.
foot and abscesses on the left calf. From the day after the operation, the fever improved and the vital signs remained stable. On the 20th day of admission, abscesses developed on the outer side of the right calf; thus, debridement was performed. Loss of soft tissue in the ulcers on the left dorsal foot did not improve, so a split-thickness skin graft was performed. The patient was discharged when the skin lesions on both lower limbs improved. During hospitalization, the patient complained of multiple arthralgia and morning stiffness, which were his previously experienced symptoms of RA. These symptoms were controlled by oral administration of acetaminophen, tramadol. After discharge, oral administration of MTX (12.5 mg/wk), methylprednisolone (4 mg/d), and tacrolimus (2 mg/d) was commenced, with the patient under outpatient follow-up observation.

DISCUSSION

RA is known to occur in individuals with a genetic predisposition due to abnormalities in immunologic tolerance, which produce autoreactive cells and induce activation of T and B lymphocytes, production of autoantibodies and secretion of various inflammatory cytokines, thus causing inflammation in synovial membranes, which in turn causes joint deformities. Cytokines associated with this occurrence of inflammation have been an important treatment target. The exact mechanism of action of the existing DMARDs, which are used in the clinical treatment of RA, on the immune system is not known. However, they are known to suppress cytotoxic T cells. Hence, their use is considered disadvantageous owing to the risk of serious adverse events. Therefore, selective suppression of the factors that play key roles in the development of diseases is important for a more effective and safer treatment. In recent years, biological agents have been widely used in clinical settings since TNF inhibitors showed a positive effect on the treatment of RA. Moreover, other biological agents with various mechanisms have continued to be developed and are in use or under clinical testing. Biological agents used in the treatment of RA are generally classified into three types according to the following targeted biological processes: Inhibition of cytokine function, inhibition of secondary signals that stimulate T cells, and inhibition of function or elimination of B cells. Among the cytokines, interleukin (IL)-6 has various biological functions and plays an important role in immune response, inflammation, acute phase response, and hematopoiesis. IL-6 induces differentiation of B lymphocytes into mature plasma cells that secrete immunoglobulin (Ig) and are involved in the growth and differentiation of T lymphocytes by inducing IL-2 and IL-2 receptors. In addition, IL-6 was identified to be associated with rheumatic diseases such as RA, juvenile arthritis, Sjögren’s syndrome, and systemic lupus erythematosus [4].

Tocilizumab is a humanized monoclonal antibody that binds with naturally existing IL-6 receptors, inhibiting the effects of IL-6. It is created by fusing the binding sites of antibody against mouse-derived human IL-6 receptors with human IgG1. In the treatment of RA, tocilizumab alone or through a combined therapy with MTX showed more significant efficacy than MTX therapy alone [5,6]. In addition, it showed a more significant efficacy than a placebo in terms of physiological functions and fatigue in patients with severe RA who do not respond well to classical DMARDs and TNF inhibitors [6]. Also, it inhibited radiological progression [7]. However, several adverse effects including infection, gastrointestinal perforation, anaphylaxis, neutropenia, thrombocytopenia, and increased liver enzyme, total cholesterol, and triglyceride levels can occur [8].

According to a controlled study with a 6-month intravenous administration of tocilizumab, anaphylaxis and other hypersensitivity reactions that require immediate cessation of treatment developed in 0.1% of the participants (3/2,644) [8]. In managing anaphylaxis and hypersensitivity reactions related to biological agents, the first
Step is the interruption of the infusion. Vital sign should be promptly assessed and if systolic blood pressure is less than or equal to 90 mmHg and/or saturation of peripheral oxygen is less than or equal to 90%, 0.3 mg of epinephrine has to be administered by intramuscular injection. Volume expansion with isotonic crystalloid solutions should be considered and if possible, the patient should lay flat on his or her back with lower extremities elevated. Adjuvant measures include intravenous administration of diphenhydramine (25 to 50 mg); methylprednisolone (0.5 to 1 mg/kg); famotidine (20 mg) [9].

For assessment of tryptase level, blood sample should be obtained in the first 30 to 120 minutes of the hypersensitivity reactions. Tryptase is a mast cell protease released in immediate IgE and non-IgE mediated reactions and it can help the evaluation of suspected hypersensitivity reactions to biological agents [9]. One limitation of this case is the fact that serum tryptase level analysis was not performed. The risk of infection, ranging from mild to severe infection, which can result in hospitalization or death, was reported to increase in patients treated with tocilizumab. When acute inflammation occurs, neutrophils form the largest component of leukocytes. As the acute inflammation resolves, the predominant part of leukocyte population changes from neutrophil to monocyte. In this way, IL-6 contributes to coordinate the innate immune system and the adaptive immune system. Furthermore, IL-6 plays central role in converting naive T cells to differentiate into T helper type 17 (Th17) cells, together with transforming growth factor-β. Th17 cells secrete high amount of IL-17, which induces the production of antimicrobial peptides (e.g., defensins) [10]. Therefore IL-6 inhibition can make the patient more vulnerable to infection. In the long term RA exposure population with tocilizumab treatment, the overall rate of serious infections was 4.7 events per 100 patient years [8]. In most cases, these infections occurred upon co-administration with immune-suppressants such as MTX or steroid, and the infections were mostly caused by upper respiratory tract infection, nasopharyngitis, or bronchitis. Meanwhile, cellulitis was relatively rare [8], and in Korea no case of cellulitis or severe sepsis after tocilizumab treatment has been reported. In this case, at the second intravenous administration of tocilizumab, the patient developed serious anaphylaxis accompanied by edema in the lower limbs. Both immunosuppression and lower limbs edema are believed to be the important risk factors of cellulitis [11]. Before admission he had taken immunosuppressant continuously and methylprednisolone were administered by intravenous injection for the management of anaphylaxis. Also the anaphylaxis can cause edema which is the result of systemic vasodilation and increased permeability of vessels due to IgE mediated hypersensitivity reaction. And the collected fluid can serve as a medium for bacteria to grow. Two cases of cellulitis after tocilizumab treatment of RA were reported in 2011 in Japan [12]. In the first case, cellulitis developed from a wound caused by a dog bite, without direct association with intravenously administered tocilizumab. In the second case, cellulitis developed after the fourth intravenous administration of tocilizumab, with no particular causes, and improved after antibiotic treatment for 7 days. This case differs from the two cases in Japan in that adverse effects developed at the beginning of the treatment and the cases rapidly progressed to sepsis despite continuous antibiotic treatment. Tocilizumab treatment is prohibited in patients with acute infections. Its advantages and disadvantages should be weighed before commencing treatment in patients with a chronic or repetitive infection. Furthermore, if a serious infection develops during tocilizumab treatment, immediate treatment discontinuation is recommended and close observation is required to detect symptoms and signs of infection during treatment [13]. In this case, tocilizumab treatment was immediately discontinued after the patient developed an infection. Bacteria that are mainly responsible for cellulitis are Streptococcus and Staphylococcus. The etiopathogenic mechanism of cellulitis is the entrance of microbes to the body through a break in the skin. In most cases, cellulitis develops in a condition where skin damage is likely to occur, such as in the presence of obesity or edema due to occlusion of veins or lymphatic vessels [13]. In patients with typical cellulitis, aspiration cytology or biopsy is not recommended in identifying the causative microorganisms. However, in patients with decreased immune function or neutropenia, β-hemolytic streptococci or staphylococci are not commonly found as the microbes responsible for cellulitis. Therefore, aspiration cytology or biopsy can be beneficial for diagnosis [13]. In this case, aspiration cytology of the lesion was performed in consideration of the patient’s depressed immunity, which resulted from the treatment of RA, and revealed Aeromonas veronii biovar sobria. Aeromonas is an oxidase-positive, facultative anaerobic, gram-negative rod-shaped bacterium that causes infection in patients with depressed immunity in most cases [14]. Therefore, in this case, we be-
lieve that the cellulitis caused by *Aeromonas veronii biovar sobria* was due to the depressed immunity of the patient by administration of MTX, steroid, and tocilizumab.

**SUMMARY**

Adverse effects of tocilizumab have not been extensively reported in Korea. In fact, this was the first case of severe anaphylaxis. Thus, this paper describes a rare case of anaphylaxis and sepsis caused by cellulitis in a patient with RA after tocilizumab treatment. Close surveillance, patient education, and further research on adverse effects such as anaphylaxis or infection that can develop after tocilizumab treatment are required.

**CONFLICT OF INTEREST**

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

**REFERENCES**