Cardiac Tamponade during Tocilizumab Therapy in a Patient with Rheumatoid Arthritis and Anti-DNA Antibody Positivity

Daisuke Miyahara¹, Yuichi Moriyama², Yuka Yamazaki², Hironobu Tanii², Yoshifumi Okano² and Harumizu Sakurada²

Abstract:
Drug-induced lupus (DIL) is a drug-mediated immune reaction with the same symptoms as that of lupus erythematosus. We herein report the first case of tocilizumab-induced lupus syndrome presenting with cardiac tamponade. A 65-year-old man presented with cough, exertional dyspnea, and chest pain after 2 months of tocilizumab therapy for rheumatoid arthritis. Echocardiography revealed marked pericardial effusion. Antinuclear antibodies and anti-double-stranded deoxyribonucleic acid antibodies were positive. The diagnosis of cardiac tamponade due to tocilizumab-induced lupus syndrome was made. He had no recurrence of pericardial effusion after tocilizumab discontinuation. Clinicians should be alert for lupus syndrome in patients receiving tocilizumab.

Key words: drug-induced lupus, tocilizumab, pericardial effusion, rheumatoid arthritis, interleukin-6, adverse effect, case report

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Introduction
Tocilizumab is a humanized murine monoclonal antibody against the interleukin-6 (IL-6) receptor. It binds to and prevents the action of IL-6 receptors present in the serum and joint fluid as well as membrane-bound IL-6 receptors on the surface of macrophages, B- and T-lymphocytes, and dendritic cells, leading to the suppression of various immunological functions (1). Tocilizumab is mainly used in the treatment of rheumatoid arthritis (RA), systemic juvenile idiopathic arthritis, and polyarticular juvenile idiopathic arthritis. It has also been investigated as a treatment for other conditions, such as Crohn’s disease, systemic lupus erythematosus, Takayasu arteritis, giant cell arteritis, polymyalgia rheumatica, and refractory adult-onset Still’s disease (2-9).

Drug-induced lupus (DIL) is a rare drug reaction presenting with the same symptoms as that of idiopathic lupus erythematosus. With the introduction of new drugs in clinical practice, an increase in the number of drug-induced illnesses has been reported. Reports implicating tocilizumab as a cause of cardiac tamponade are scarce in the literature. Furthermore, there have been no reports on tocilizumab-induced lupus syndrome.

We herein report a 65-year-old patient who developed cardiac tamponade associated with DIL during tocilizumab treatment. To our knowledge, this is the first reported case of tocilizumab-induced lupus syndrome presenting with cardiac tamponade.

Case Report
A 65-year-old man with RA was started on tocilizumab. He presented with stiffness of both hands and had been diagnosed with RA at 64 years of age. He was treated with methotrexate (MTX) and a low dose of prednisolone (PSL). However, stiffness of both hands persisted. At 65 years of age, the subcutaneous administration of tocilizumab every 2
Table. Laboratory Findings on Admission.

| Complete blood count | Biochemistry | Serology |
|----------------------|--------------|----------|
| WBC 14,900 /μL      | TP 7.1 g/dL  | CRP 15.7 mg/dL |
| Neutrophil 87.1 %   | Alb 3.6 g/dL | RF 968 IU/mL  |
| Lymphocyte 5.2 %    | T-Bil 2.7 g/dL | C3 64 mg/dL |
| Monocyte 7.4 %      | AST 162 IU/L | C4 8 mg/dL  |
| Eosinophil 0.0 %    | ALT 113 IU/L | CH50 <10 U/mL|
| RBC 4.10×10^6 /μL  | LDH 379 IU/L | IgG 1.593 mg/dL|
| Hb 12.3 g/dL        | CK 67 IU/L  | IgA 287 mg/dL |
| MCV 93.8 fL         | CK-MB 5 IU/L | IgM 166 mg/dL |
| MCH 30.1 pg         | Trop-1 11.1 pg/mL | ANA 160x (homo, spe) |
| Hct 38.4 %          | Cr 0.62 mg/dL | ACPA >1,200 U/mL |
| Plt 35.5×10^4 /μL  | BUN 18.8 mg/dL | a-SS-A Ab <1.0 U/mL |
|                     | Na 132 mEq/L  | a-SS-B Ab <1.0 U/mL |
|                     | K 4.2 mEq/L  | a-ssDNA Ab 37.2 A/U/mL |
|                     | BNP 32.4 pg/mL | a-DsDNA Ab 37.3 IU/mL |
|                     |               | a-Sm Ab <1.0 U/mL |
|                     |               | a-RNP Ab <2.0 U/mL |
|                     |               | a-CL-IgG <8.0 U/mL |
|                     |               | a-CLβ2GPI Ab <3.5 U/mL |
|                     |               | Syphilis RPR negative |

Boldface indicates abnormal values.

WBC: white blood cell, RBC: red blood cell, Hb: hemoglobin, MCV: mean corpuscular volume, MCH: mean corpuscular hemoglobin, Hct: hematocrit, Plt: platelet, TP: total protein, Alb: albumin, T-Bil: total bilirubin, AST: aspartate aminotransferase, ALT: alanine aminotransferase, LDH: lactate dehydrogenase, Cr: creatinine, BUN: blood urea nitrogen, CRP: C-reactive protein, RF: rheumatoid factor, Ig: immunoglobulin, ANA: anti-nuclear antibodies, ACPA: anti-citrullinated protein antibody, a- : anti, Ab: antibody, SS: Sjögren’s syndrome, ss: single-stranded, ds: double-stranded, RNP: ribonucleoprotein, Sm: Smith, CL: cardiolipin.

Figure 1. Chest X-ray findings.

weeks was added. After two months of therapy, he presented to the emergency department with exertional dyspnea and chest pain. The patient also reported a cough that had started after the initiation of tocilizumab therapy. His medical history included effort angina. There was no family history of autoimmune disease. His regular medications included celecoxib, MTX, foliamine, rosuvastatin, prasugrel, esomeprazole, nicorandil, and isosorbide mononitrate.

At the presentation, his blood pressure was 129/93 mmHg, pulse was 108/min, respiratory rate was 28/min with an O₂ saturation of 95% on room air, and body temperature was 37.9°C. He was orthopneic at rest, and his lungs were clear on auscultation. His jugular venous pressure was elevated, and heart sounds were normal with no murmurs. He presented with a painful oral ulcer. There was no evidence of skin rash, rheumatoid nodules, or arthralgia. On admission, initial investigations revealed leukocytosis (white cell count 14,900/μL, neutrophils 87.1%, lymphocytes 5.2%, monocytes 7.4%, eosinophils 0%, basophils 0.3%), hemoglobin of 12.3 g/dL, and platelet count of 355,000/μL. His renal function, electrolytes, cardiac enzymes, and thyroid-stimulating hormone levels were normal. However, inflammatory markers (C-reactive protein 15.71 mg/dL) and liver function test results (albumin 3.6 g/dL, bilirubin 2.7 mg/dL, alkaline phosphatase 162 IU/L, alanine transaminase 113 IU/L, and lactate dehydrogenase 379 IU/L) were found to be abnormal (Table).

Chest radiography revealed cardiac enlargement (Fig. 1), and chest computed tomography showed marked pericardial effusion and slight left-sided pleural effusion (Fig. 2). An electrocardiogram revealed PR elevation in aVR and an abnormal Q wave in leads V1-2. Transthoracic echocardiography revealed marked pericardial effusion and collapse of the right atrium and ventricle (Fig. 3). The patient was thus diagnosed with cardiac tamponade.

Pericardiocentesis was performed, and 900 mL of fluid was drained. Pericardial fluid cytology revealed cells with an inflammatory response. Culture of the pericardial effu-
Discussion

DIL is a drug-mediated immune reaction that leads to clinical features similar to those of idiopathic lupus. It usually presents after months or years of continuous exposure to an offending drug (11). Numerous medications have been implicated in the development of DIL. Antitumor necrosis factor (TNF)-α therapy is a treatments for RA and has recently been reported to induce DIL, thus spurring several discussions concerning the mechanism underlying DIL. Tocilizumab is an anti-IL-6 receptor antibody. Both anti-IL-6 receptor antibodies and anti-TNF-α drugs are used as RA treatments. There have been no reported cases of anti-IL-6 therapy-associated DIL, although several cases of anti-TNF-α therapy-associated DIL have been reported. The common clinical presentations of DIL include arthralgia, arthritis, myalgia, a fever, and weight loss. Pericardial effusion due to DIL is relatively uncommon.

Ozaki et al. reported a case of cardiac pericarditis as an adverse effect of tocilizumab (12). This case was negative for antinuclear antibodies and was not diagnosed as DIL. In addition, they concluded that the pericardial effusion associated with RA had increased rapidly before tocilizumab could prove its efficacy, suggesting it might not be an adverse effect of tocilizumab.

In our case, the patient had severe pericardial effusion, and anti-dsDNA antibody titers were elevated during tocilizumab therapy. Therefore, we decided to stop administering the drug, after which the patient’s titer gradually decreased to normal without additional treatment for RA. Regarding the effusion, we performed pericardiocentesis and drained 900 ml of fluid; no re-effusion was recognized in the next 12 months. These findings confirmed our diagnosis of tocilizumab-induced lupus.

His clinical and laboratory manifestations (serositis [pericarditis and pleuritic], RF, and hypocomplementemia) were also considered to meet the criteria for rheumatoid vasculitis. The pericardial effusion might have been a result of malignancy. A dominant increase in virus antibodies was absent on a blood test. Connective tissue disease workup showed positivity for antinuclear antibodies (ANAs) with a titer of 1:160, and the anti-double-stranded deoxyribonucleic acid antibody (anti-dsDNA) titer was elevated at 37.2 U/mL. Regarding complement (C) levels, the C3 level was low at 64 mg/dL, the C4 level was low at 8 mg/dL, and the CH50 level was less than 10 mg/dL.

His clinical and laboratory manifestations (serositis [pericarditis and pleuritic], ANA positivity, hypocomplementemia, and anti-dsDNA antibody positivity) were considered to fulfill the Systemic Lupus Collaborating Clinics (SLICC) 2012 criteria for systemic lupus erythematosus (SLE) (10).

We discontinued tocilizumab and prescribed colchicine and nonsteroidal anti-inflammatory drugs on admission. He was only treated with MTX for RA. He had no recurrence of pericardial effusion in the next 12 months, and the serum levels of anti-dsDNA antibodies gradually decreased.

Written informed consent was obtained from the patient for the publication of this case report and its accompanying images.

Several lines of evidence indicate that type I IFN, espe-
ically IFN-α, plays a central role in the pathogenesis of SLE (18). After tocilizumab administration in patients with RA and Castleman disease, IL-6 receptors are saturated with tocilizumab, and IL-6 signaling is completely inhibited, but the serum levels of both IL-6 and IL-6 receptor are markedly increased; this suggests that various cytokines, including IFNs, might also be upregulated under tocilizumab treatment (19). We hypothesized that this mechanism may be responsible for the development of SLE during tocilizumab treatment.

We herein report the first case of tocilizumab-induced lupus with cardiac tamponade. Clinicians should be alert for lupus syndrome, which can present with medical emergencies, such as cardiac tamponade, in patients receiving tocilizumab.

The authors state that they have no Conflict of Interest (COI).

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