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【 CASE REPORT 】

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

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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 weeks was added. After two months of therapy, he presented to the emergency department with exertional dyspnea and

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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-I	11.1 pg/mL	**ANA**	**160× (homo, spe)**
Hct	**38.4 %**	Cr	0.62 mg/dL	**ACPA**	**>1,200 U/mL**
Plt	**35.5×104 /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 AU/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-CL·β2GPI 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: lactic 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.

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 O_2 saturation of 95% on room air, and body temperature was 37.9℃. 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 effusion was negative for bacterial, mycobacterial, and fungal infections. There was no evidence of malignancy. A domi-

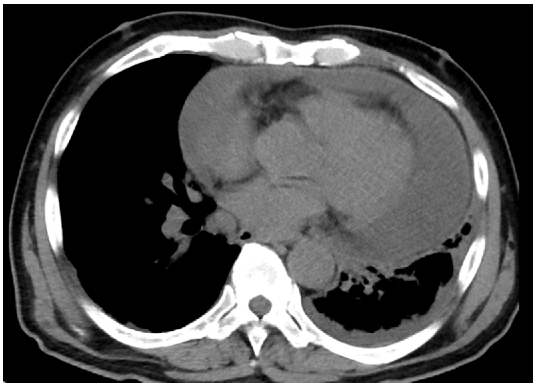

Figure 2. **Chest computed tomography (CT) findings. Chest CT showing a large pericardial effusion with a small left-sided pleural effusion.**

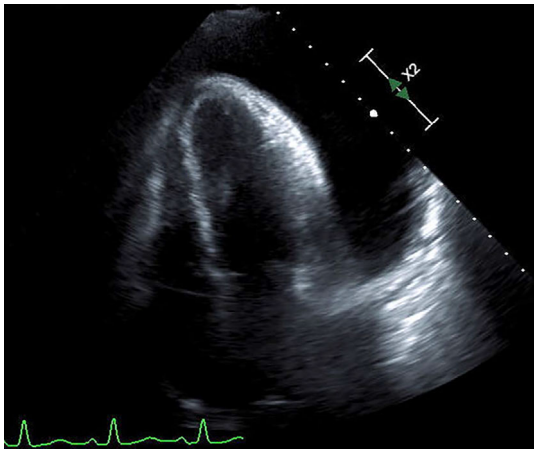

Figure 3. **Echocardiogram findings.**

nant 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 International 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 (Fig. 4).

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

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. Anti-tumor 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 malignant RA. However, the patient had a short duration of RA, and RA had progressed without exacerbation after tocilizumab treatment. In addition, when we stopped administrating tocilizumab, pericarditis did not recur. The development of SLE secondary to tocilizumab therapy has not yet been reported. We believe that anti-dsDNA antibodies might have triggered lupus in this case. Anti-dsDNA antibodies are typically absent in DIL; however, they can sometimes be found in interferon (IFN)-α- and anti-TNF-α-induced lupus (13, 14). A few mechanisms have been proposed concerning the development of SLE during anti-TNF-α therapy (15). The mechanism involved in the production of anti-dsDNA antibodies is that systemic inhibition of TNF-α might interfere with apoptosis, affecting the clearance of nuclear debris and apoptotic neutrophils by phagocytes, thus promoting the production of autoantibodies to DNA and other nuclear antigens (14, 16, 17).

Several lines of evidence indicate that type I IFN, espe-

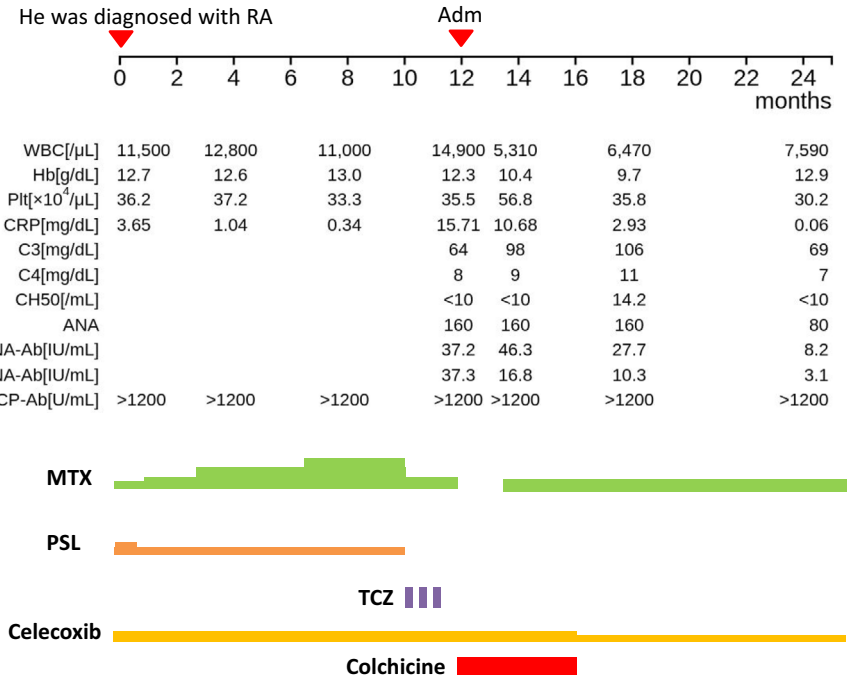

Figure 4. Clinical course. The clinical course of this patient is summarized as indicated. a-CCP-Ab: anti-cyclic citrullinated peptide antibody, a-ssDNAAb: anti-single-stranded DNA antibody, a-dsDNA-Ab: anti-double-stranded DNA antibody, ANA: anti-nuclear antibody, Hb: hemoglobin, MTX: methotrexate, Plt: platelet, PSL prednisolone, TCZ: tocilizumab, WBC: white blood cell

cially 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).

References

1. Mihara M, Kasutani K, Okazaki M, et al. Tocilizumab inhibits signal transduction mediated by both mIL-6R and sIL-6R, but not by the receptors of other membranes of IL-6 cytokine family. Int Immunopharmacol **5**: 1731-1740, 2005.
2. Ito H, Takazoe M, Fukuda Y, et al. A pilot randomized trial of a human anti-interleukin-6 receptor monoclonal antibody in active Crohn's disease. Gastroenterology **126**: 989-996; discussion 947, 2004.
3. Illei GG, Shirota Y, Yarboro CH, et al. Tocilizumab in systemic lupus erythematosus: Data on safety, preliminary efficacy, and impact on circulating plasma cells from an open-label phase I dosage-escalation study. Arthritis Rheum **62**: 542-552, 2010.
4. Abisror N, Mekinian A, Lavigne C, et al. Tocilizumab in refractory Takayasu arteritis: a case series and updated literature review. Autoimmun Rev **12**: 1143-1149, 2013.
5. Stone JH, Tuckwell K, Dimonaco S, et al. Efficacy and safety of tocilizumab in patients with giant cell arteritis: primary and secondary outcomes from a phase 3, randomized, double-blind, placebo-controlled trial [abstract]. Arthritis Rheumatol **68** (Suppl): 2016.
6. Hagihara K, Kawase I, Tanaka T, Kishimoto T. Tocilizumab ameliorates clinical symptoms in polymyalgia rheumatica. J Rheumatol **37**: 1075-1076, 2010.
7. Thonhofer R, Hiller M, Just H, Trummer M, Siegel C, Dejaco C. Treatment of refractory adult-onset still's disease with tocilizumab: report of two cases and review of the literature. Rheumatol Int **31**: 1653-1656, 2011.
8. Iwamoto M, Nara H, Hirata D, Minota S, Nishimoto N, Yoshizaki K. Humanized monoclonal anti-interleukin-6 receptor antibody for treatment of intractable adult-onset Still's disease. Arthritis Rheum **46**: 3388-3389, 2002.
9. Matsumoto K, Nagashima T, Takatori S, et al. Glucocorticoid and cyclosporine refractory adult onset Still's disease successfully treated with tocilizumab. Clin Rheumatol **28**: 485-487, 2009.
10. Petri M, Orbai AM, Alarcón GS, et al. Derivation and validation of the Systemic Lupus International Collaborating Clinics classification criteria for systemic lupus erythematosus. Arthritis Rheum **64**: 2677-2686, 2012.
11. Borchers AT, Keen CL, Gershwin ME. Drug-induced lupus. Ann N Y Acad Sci **1108**: 166-182, 2007.
12. Ozaki Y, Tanaka A, Shimamoto K, et al. A case of rheumatoid pericarditis associated with a high IL-6 titer in the pericardial fluid and tocilizumab treatment. Mod Rheumatol **21**: 302-304, 2011.
13. Bandt MD. Lessons for lupus from tumor necrosis factor blockade. Lupus **15**: 762-767, 2006.
14. Eriksson C, Engstrand S, Sundqvist KG, Rantapää-Dahlqvist S. Autoantibody formation in patients with rheumatoid arthritis

treated with anti-TNF alpha. Ann Rheum Dis **64**: 403-407, 2005.
15. Emma L. Williams, Stephan G, Chrisopher J. Edwards. Anti-TNF-induced lupus. Rheumatology (Oxford) **48**: 716-720, 2009.
16. Bickerstaff MC, Botto M, Hutchinson WL, et al. Serum amyloid P component controls chromatin degradation and prevents antinuclear autoimmunity. Nat Med **5**: 694-697, 1999.
17. Lorenz HM, Herrmann M, Winkler T, Gaipl U, Kalden JR. Role of apoptosis in autoimmunity. Apoptosis **5**: 443-449, 2000.
18. Thorlacius GE, Wahren-Herlenius M, Rönnblom L. An update on the role of type I interferons in systemic lupus erythematosus and Sjögren's syndrome. Curr Opin Rheumatol **30**: 471-481, 2018.
19. Nishimoto N, Terao K, Mima T, Nakahara H, Takagi N, Kakehi T. Mechanisms and pathologic significances in increase in serum interleukin-6 (IL-6) and soluble IL-6 receptor after administration of an anti-IL-6 receptor antibody, tocilizumab, in patients with rheumatoid arthritis and Castleman disease. Blood **112**: 3959-3964, 2008.