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CASE REPORT

A case of rheumatoid pericarditis associated with a high IL-6 titer in the pericardial fluid and tocilizumab treatment

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Abstract We report a 60-year-old woman with rheumatoid arthritis complicated by pericarditis. Treatment with tocilizumab improved her polyarthritis, but the pericardial effusion increased so rapidly as to cause cardiac tamponade before the treatment could prove its efficacy. Pericardial effusion disappeared after pericardiocentesis. The pericardial fluid contained a remarkably high concentration of interleukin-6 (IL-6; 351,000 pg/mL), which tocilizumab appeared to have made yet higher compared to the reported IL-6 levels in rheumatoid pericarditis. No further exacerbation of pericarditis was observed after retreatment with tocilizumab. This case has important implications in that it suggests that the prominently elevated IL-6 level in pericardial fluid during tocilizumab treatment may be an indicator of its efficacy for pericarditis.

Keywords Interleukin-6 · Pericarditis · Rheumatoid arthritis · Tocilizumab

Introduction

Tocilizumab is a humanized anti-interleukin-6 (IL-6) receptor monoclonal antibody that is efficacious in the treatment of rheumatoid arthritis (RA). It not only alleviates the signs and symptoms of RA but also prevents progressive bone and joint destruction [1]. RA patients are known to develop pericarditis as a complication, although severe pericarditis is rare clinically [2]. Here, we report a case of pericarditis that deteriorated after commencement of tocilizumab treatment for active RA. The pericarditis in this case appeared not to be an adverse effect of tocilizumab, as no further exacerbation of pericarditis occurred after reinstatement of the tocilizumab treatment. This case is important in that it implies that a significantly elevated IL-6 level in pericardial fluid during tocilizumab treatment may be an indicator of its efficacy for pericarditis.

Case report

A 60-year-old Japanese woman with RA had been treated with gold sodium thiomalate after the initial diagnosis of RA at the age of 33 years. She had no history of pleuritis or pericarditis. However, her treatment was interrupted by urticaria due to gold sodium thiomalate. As her symptoms were slight, she was left untreated thereafter. At age 55 years, she was diagnosed with moderate pericardial effusion caused by RA based on chest radiographic and echographic findings. At this time, treatment with several disease-modifying anti-rheumatic drugs, including anti-tumor necrosis factor (TNF) antibody (salazosulfapyridine, bucillamine, mizoribine, tacrolimus, methotrexate, infliximab, etanercept), was initiated to treat her RA, but these agents were ineffective. At age 60 years, she was started on tocilizumab. Based on the 28-joint Disease Activity Score calculated using erythrocyte sedimentation rate with four outcome parameters [DAS-28(ESR 4)] on day 14 (8.59 → 4.09) (tender joint count: 20 → 1; swollen joint count: 8 → 2;

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global assessment of visual analog scale: 92 → 37 mm; C-reactive protein: 6.733 → 0.074; ESR: 106.7 → 41.7), the treatment appeared to be effective. However, chest pain emerged on day 17, and the patient was hospitalized.

The results of the physical examination on admission were: body temperature, 37.2°C; blood pressure, 100/65 mmHg; pulse rate, 111 beats/min and regular; percutaneous oxygen saturation of arterial blood, 93% (room air). Chest radiography revealed severe cardiomegaly with moderate pulmonary congestion. Electrocardiography showed sinus tachycardia and ST-T elevation in II, III, aVF, and V3–V6. Echocardiography showed massive pericardial effusion around the heart with slight diastolic collapse of the right ventricle (Fig. 1).

The results of laboratory tests were: white blood cell count, 15.7 × 10^3/mm^3 (91.7% neutrophils, 5.5% lymphocytes); red blood cell count, 3.68 × 10^6/mm^3; hemoglobin concentration, 8.7 g/dL; hematocrit, 30.0%; platelet count, 19.3 × 10^4/mm^3; aspartate aminotransferase, 102 IU/L; alanine aminotransferase, 30 IU/L; lactate dehydrogenase, 369 IU/L; blood urea nitrogen, 23 mg/dL; creatine kinase, 0.61 mg/dL; C-reactive protein, 1.030 mg/dL; cardiac troponin I, 0.08 ng/mL; N-terminal pro B-type natriuretic peptide, 925.2 pg/mL; matrix metalloproteinase-3, 110.4 ng/mL; 50% hemolytic unit of complement (CH50), 45 U/mL; rheumatoid factor, 36 IU/mL; and she was negative for anti-nuclear antibody.

The patient was diagnosed with cardiac tamponade due to pericarditis, and pericardial drainage was performed. Laboratory testing of the pericardiac fluid revealed 125 mg/dL glucose, 5.1 g/dL total protein, and 1022 IU/L lactate dehydrogenase. Microbial and cytological examination of the pericardiac fluid showed neither bacterial infection nor malignancy. IL-6 was measured in both the serum and pericardiac fluid. As shown in Table 1, the IL-6 levels were remarkably high in both the serum (3,420 pg/mL) and fluid (351,000 pg/mL).

On the third hospital day, cardiac tamponade had been improved by drainage, and the patient was discharged on day 14. She was subsequently treated with methotrexate alone (4 mg/week) to verify disappearance of the pericardial effusion, but her RA worsened within 2 months. With the patient's consent, tocilizumab treatment was restarted concomitant with discontinuance of methotrexate. The patient's RA activity was immediately ameliorated by tocilizumab and has since been controlled for 2 years following the readministration of tocilizumab treatment without further exacerbation of pericarditis.

Discussion

The patient described here had multidrug-resistant RA, which responded only to tocilizumab. Pericarditis, including asymptomatic cases, is a relatively frequent complication of RA [2], and in this patient, there was stable pericardial effusion without any evidence of heart failure. We therefore initiated therapy with tocilizumab. However, the pericardial effusion increased so rapidly as to cause cardiac tamponade before the tocilizumab could prove its efficacy—although tocilizumab had improved her polyarthritis. This is the first report of pericarditis as an adverse effect of tocilizumab treatment. As may be inferred from the lack of any further exacerbation of pericarditis in the 2 years since tocilizumab treatment was restarted, the worsening of pericarditis at this time appeared not to be an adverse effect of tocilizumab. It is also possible that the pericarditis in our patient was ameliorated by the tocilizumab treatment but that the delay of absorption of pericardial effusion led to cardiac tamponade.

Both subjective and objective symptoms were improved by tocilizumab treatment at the early stage and, therefore, we consider the tocilizumab treatment to have been

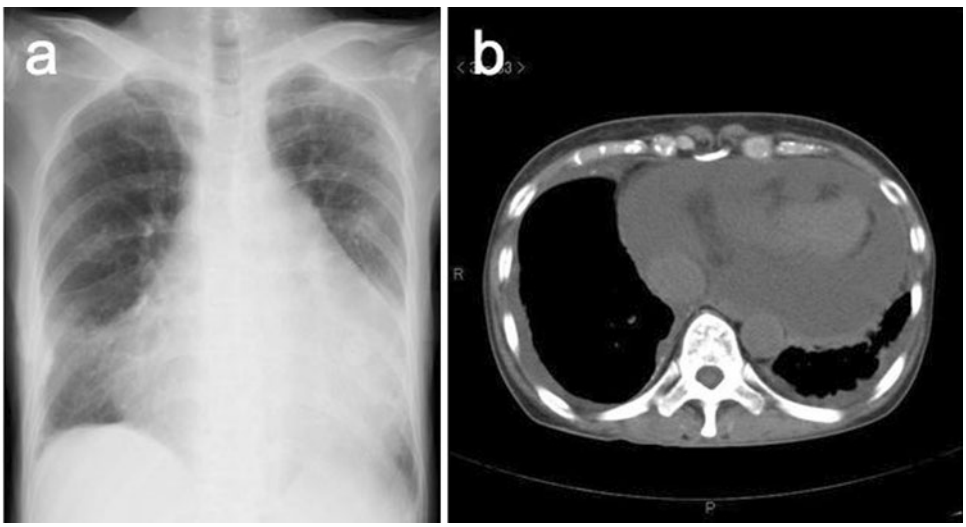

Fig. 1 Chest X-ray and computed tomography (CT) at admission. **a** Chest X-ray revealing enlargement of the cardiac silhouette, **b** chest CT scan showing pericardial fluid around the whole heart

Table 1 Time course of treatment in terms of levels of disease-modifying anti-rheumatic drugs

	Before TCZ administration	On admission	Before MTX administration	Before TCZ readministration	After TCZ readministration
Days after the first TCZ administration	0	17	27	93	111
DAS 28(ESR 4)	8.59	4.09[a]	5.96	7.29	3.28
IL-6					
Serum	90 pg/mL	3,420 pg/mL	23 pg/mL	ND	ND
Pericardial fluid	ND	351,000 pg/mL	ND	ND	ND
TNFα					
Serum	340 pg/mL	1.9 pg/mL	ND	ND	ND
IL-2					
Serum	155 U/mL	27 U/mL	ND	ND	ND

DAS disease activity score, *ESR* erythrocyte sedimentation rate, *IL* interleukin, *TNF* tumor necrosis factor, *ND* not done, *TCZ* tocilizumab, *MTX* methotrexate

[a] Tested 14 days after the first TCZ administration

effective against arthritis. As shown in Table 1, the serum TNFα level, which is proportional to the RA activity [3], indeed decreased after the administration of tocilizumab.

Shikama et al. [4] reported high levels of IL-6 in pericardial fluid in a patient with RA-mediated pericarditis. Based on this find, they suggested that an evaluation and correction of dysregulated IL-6 production is a useful marker in the diagnosis and treatment of rheumatoid pericarditis. Others studies have reported that the concentration of IL-6 in the pericardial fluid was 1,670 pg/mL in a systemic lupus erythematosus patient, 2,950 pg/mL in a patient with RA, and 2,296.8 pg/mL in a patient with viral infection [4–6]. In our patient, the IL-6 level in the pericardial fluid was much higher, namely, 351,000 pg/mL, than those reported in these studies.

Tocilizumab binds to the IL-6 binding site of human IL-6R and competitively inhibits IL-6 signaling. Nishimoto et al. [7] reported that the serum IL-6 levels in patients with RA increased markedly on day 14 of tocilizumab administration. They further suggested that the serum IL-6 level is dependent on the balance between the production and clearance of IL-6 and that tocilizumab blocks IL-6R-mediated clearance. In this context, tocilizumab may cause increases in serum and pericardial fluid IL-6 by inhibiting IL-6R-mediated clearance. In our patient, the serum cytokine data before and after the administration of tocilizumab are in agreement with the results of Nishimoto et al. [7] (Table 1). The remarkably high IL-6 level in the pericardial fluid in our patient suggests the effective concentration of tocilizumab and its binding to IL-6 receptors in the fluid. We therefore suggest that the extraordinarily high level of IL-6 in pericardial fluid paradoxically implies that tocilizumab is effective against rheumatoid pericarditis. It is possible that there is different effect on the extra-articular manifestations of RA between anti-TNF and IL-6 therapy.

Conflict of interest None.

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