Fatal Complication of *Legionella pneumophila* Pneumonia in a Tocilizumab-treated Rheumatoid Arthritis Patient

Yoshiyuki Arinuma¹, Shinichi Nogi¹, Yuichi Ishikawa¹, Hisanori Nakayama¹, Atsushi Hashimoto¹, Akiko Komiya², Kenji Minoguchi³, Ayako Horita¹, Ikuo Saito⁴, Toshihiro Matsui¹ and Shigeto Tohma⁵

Abstract

We herein report a fatal case of *Legionella pneumophila* pneumonia in a tocilizumab-treated rheumatoid arthritis patient who was in a state of shock on admission but remained afebrile even during severe pneumonia. *Legionella* antigen was detected in the urine and neutrophil CD64 expression was highly elevated. Despite undergoing intensive treatment, the patient developed sepsis and died 12 days after admission. An autopsy indicated that while the *Legionella* infection had almost been controlled, a subarachnoid hemorrhage was the ultimate cause of death.

Key words: *Legionella*, rheumatoid arthritis, tocilizumab, biologics, neutrophil CD64

(Intern Med 54: 1125-1130, 2015)  
(DOI: 10.2169/internalmedicine.54.3103)

Introduction

Treat to target (T2T) is proposed as a means to manage rheumatoid arthritis (RA) more effectively to prevent joint destruction (1). Recently, the classification and remission criteria of RA have been established for T2T (2, 3). To achieve remission or low disease activity, biologic disease-modifying antirheumatic drugs (biologics) as well as methotrexate (MTX) are employed (4). Tumor necrosis factor-inhibitors (TNF-I) are major biologics (5) and many other biologics targeting other molecules are currently being developed.

Tocilizumab (TCZ), an antibody against the interleukin (IL)-6 receptor, blocks IL-6 signaling, suppressing the production of acute phase reactants and fever (6). Therefore, there is concern about TCZ treatment masking the signs of infection. It has been reported that the use of biologics increases the incidence of infection, particularly lower respiratory tract infections (7). The use of TCZ also significantly increases the risk of serious respiratory infections (8, 9), the standardized incidence rate of which was reported to be 3.64 with a 95% confidence interval of 2.56-5.01 per 100 patient-years (10). *Legionella* pneumonia, an opportunistic infection, has been reported in patients treated with TNF-I (11-14) but not with TCZ. We herein report an RA patient who developed severe pneumonia caused by *Legionella pneumophila* under treatment with TCZ.

Case Report

A 64-year-old man had suffered from RA since 1996 and had undergone right total knee arthroplasty in 2003. He had been taking antirheumatic drugs, such as bucillamine and MTX, but they were discontinued due to adverse events (nephritic syndrome and interstitial pneumonia, respectively). His disease could not be controlled with low dose...
prednisolone (PSL) treatment alone; hence, etanercept (ETN) (50 mg/week) was started in April 2009. ETN administration led to remission but had to be discontinued due to the occurrence of urticarial rashes. Next, adalimumab (ADA) (40 mg/2 weeks) was tried, but it was also discontinued due to skin lesions. We then stopped targeting TNF-1 and started TCZ treatment in June 2009. A low dose of cyclosporin (CyA) (50 mg/day) was also administered for complicated rheumatoid neutrophilic dermatitis after the first administration of TCZ. The patient’s RA and skin lesion disease activity became well controlled with PSL (6 mg/day), CyA (50 mg/day) and TCZ (8 mg/kg) every 4 weeks, and the patient’s Disease Activity Score in 28 joints (DAS28-ESR) (15) and the Clinical Disease Activity Index (CDAI) (16) were 1.79 (remission) and 3.22 (low disease activity), respectively. The patient had no family history of rheumatic disease. He had been smoking 20 cigarettes a day since he was 20 years old. He and his family did not use a recirculating bathing system.

The patient had felt general fatigue beginning the evening of late in July, 2011 and dyspnea the following morning. After two days, he was admitted to our hospital’s emergency section for progressive dyspnea and severe appetite loss. On admission, his body temperature was 36.8°C and blood pressure was 70/40 mmHg with a pulse rate of 102 beats per minute. His blood oxygen saturation using pulse oximetry was 90% in an oxygen flow of 10 L/min via a mask. His Glasgow Coma Scale was 14; eye opening 3, verbal response 5, and motor response 6. A physical examination revealed mild coarse crackles in the right chest and slight fine crackles in both the left and right sides. The laboratory testing results were as follows: red blood cell count 462×10^12/mm^3, hematocrit 40.6%, hemoglobin 14.6 g/dL, white blood cell count 9,070/mm^3 (90% neutrophils, 4% lymphocytes, and 1% eosinophils) and platelet count 8.8×10^12/mm^3. The arterial blood gas analysis (BGA) was: pH 7.452, PaO2 65.4 Torr, PaCO2 27.6 Torr and base excess -3.3 mmol/L. The patient’s arterial BGA showed PaO2 79.0 Torr with FiO2 1.0 (P/F ratio: 79) under a positive end-expiratory pressure of 10 cm H2O, reflecting severe respiratory failure. Urine testing for pneumococcus antigen was negative but positive for Legionella (BinaxNOW®, Alere, Tokyo, Japan). No significant pathogens were identified in the sputum and urine smears. We diagnosed the patient with Legionella pneumonia complicated with acute respiratory distress syndrome (ARDS), satisfying the Berlin definition as severe ARDS (18) with shock. The patient was started on antibiotic therapy with pafuzloxacin (2,000 mg/day) and erythromycin (1,000 mg/day) together with steroid pulse therapy (methylprednisolone, 1,000 mg/day for 3 days) and sivelestat sodium hydrate for ARDS. Additionally, antithrombin III and low-molecular-weight heparin were administered for suspected disseminated intravascular coagulation. Nevertheless, the patient’s respiratory failure gradually worsened with progression of pneumonia shadow on chest X-ray and CT (Fig. 2). On the fourth day following admission, the patient’s neutrophil CD64 levels decreased (21,071 molecules/cell) as well as his CRP level (7.67 mg/dL). However, on the fifth day, the patient developed a high grade fever accompanied by tachycardia with the loss of the pupillary light reflex. His neutrophil CD64 expression once again elevated (23,939 molecules); however, his CRP level decreased (4.62 mg/dL). Methicillin-resistant Staphylococcus aureus (MRSA) was identified in both samples collected from his blood and the catheter edge of the central venous line; accordingly, teicoplanin treatment was started. Rifampicin was added as well as an endotoxin-adsorption therapy against Legionella pneumonia pneumonia; however, the patient’s respiratory failure did not improve and he expired 12 days after admission. A post-mortem polymerase chain reaction (PCR) test on a sputum specimen was found to be positive for Legionella pneumonia, serogroup 1.

An autopsy was carried out 24 hours after death. Very few inflammatory lesions where neutrophils phagocytosed gram-negative bacilli in the lung could be identified by histopathology (Fig. 3). Staphylococcal abscesses were present in multiple organs (lungs, heart, kidneys and spleen) (Fig. 4) and a subarachnoid hemorrhage (SAH) caused by rupture of the abscesses was found at the spine level (Fig. 5). An intracranial examination was not permitted. There was no evidence of interstitial pneumonia but there
were significant emphysematous changes in the lungs.

**Discussion**

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According to data from clinical trials and post-marketing surveillance, RA patients on TCZ ther-

Figure 3. Microscopic manifestations. (A) Emphysematous changes with a few inflammatory le-

Figure 4. Representative features of abscesses. (A) A small artery in the lung occluded by staphylo-

Figure 5. Axial section of spinal cord. A hemorrhage is shown under the subarachnoid space (H&E staining, ×10 magnification).

ra-tory tract infections (8-10). Previously, severe bacterial pneumonia cases were reported in RA patients receiving TCZ therapy (19). However, to the best of our knowledge, no previous reports of Legionella infection in RA patients receiving TCZ (in recent PubMed search results) exist. Menéndez et al. reported that serum IL-6, as well as TNF-α levels in patients with Legionella pneumonia, were higher among patients with community-acquired pneumonia other than Legionella pneumonia (20). In vitro, induction and ex-

expression of IL-6 derived from lung epithelial cells increased after invasion of human alveolar cells by Legionella pneumophila, thus indicating that IL-6 is required for normal de-

Thus, this mechanism might be one of the pathogenic factors exacerbating Legionella pneumonia in RA patients treated with TCZ. However, this does not seem to be the case with TNF-I treatment.

A characteristic of our patient was that his initial symp-
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v ere infection. Another intriguing finding was that his CRP level was highly elevated despite well-controlled RA under the TCZ therapy. It is concerning that TCZ may prevent fe-

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TCZ therapy. However, all of the eight patients with RA in this database recovered, in contrast to our patient (13). TCZ is another available bio-

logic for RA, exerting its effects by blocking IL-6 signaling and thus inhibiting the inflammatory pathway, resulting in reduced fever and reduced production of acute phase reac-

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tions led to significant increases in CRP levels even in TCZ users (22). In addition, such patients often feel general fatigue even without fever or other infectious symptoms during severe infections. Therefore, the elevation of CRP together with general fatigue may be an important initial sign of masked severe infection in TCZ users.

We previously reported that peripheral blood neutrophil expression of CD64 is useful for detecting infection in patients with RA and can be used to distinguish infection from an RA flare (17). Neutrophil CD64 expression is upregulated during infection with various pathogens (e.g., bacteria, viruses, fungi and mycobacteria) but is not affected by RA disease activity or by the use of corticosteroids, disease-modifying antirheumatic drugs or biologics (17). The utility of neutrophil CD64 measurements had already been confirmed even in TCZ users (23). In the present case, the patient’s neutrophil CD64 expression was highly elevated (up to 35,749 molecules/cell) even without fever on admission, which indicated the possibility of masked severe infection. Quantitative measurements of neutrophil CD64 expression may be performed easily and rapidly (within 1 hour by our modified protocol) and we routinely measure it every day. However, it is not currently widely available in routine laboratory analysis because access to flow cytometry is required. PCT is also well-known and utilized as a useful biomarker related to the severity of bacterial infections and sepsis (24) and may be increased during Legionella infection (20, 25, 26) as also seen in the present case. However, it should be noted that PCT may not be upregulated during viral or mycobacterial infections, unlike neutrophil CD64. Therefore, simultaneous measurement of neutrophil CD64 and PCT may be helpful to differentiate between pathogens.

Pulmonary damage due to Legionella pneumophila pneumonia, as judged by histopathology, was limited in the present case. However, staphylococcal abscesses were detected in multiple organs due to MRSA sepsis, which may have developed into brain aneurysms. Because MRSA were not detected in any specimens collected on admission, MRSA sepsis must have developed as a nosocomial infection associated with catheter use. The autopsy data indicated that the Legionella infection had almost been controlled and that a subarachnoid hemorrhage due to a ruptured aneurysm was the ultimate cause of death. These complications, such as MRSA sepsis, infectious aneurysms and subarachnoid hemorrhage, may have developed due to excessive immunosuppression (including repeated steroid pulse therapies) for severe pulmonary infection and respiratory failure.

In summary, this is the first case report of Legionella pneumophila pneumonia in a RA patient being treated with TCZ. Infectious signs and symptoms are often masked or modified by TCZ, but this case indicated that elevation of CRP levels with general fatigue may be a sign of severe infection. Furthermore, the level of neutrophil CD64 expression may help detect infection even without fever during TCZ therapy. When administering TCZ, we must be careful not to miss the signs and symptoms of infection taking the characteristics of TCZ into account.

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

References


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