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Fulminant Pulmonary Tuberculosis by Infliximab in Patient with Rheumatoid Arthritis

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Abstract

A 72-year-old Japanese woman who had been suffering from rheumatoid arthritis for five years started treatment with infliximab. The screening of a chest X-ray before initiating infliximab treatment showed no abnormal shadows. After a month of infliximab, she was admitted to the emergency hospital with a half-month history of a fever, fatigue, dyspnea, and cough. She was diagnosed with tuberculosis from a culture smear and referred to our hospital. The chest images showed a bilateral massive cavity and infiltration. Despite the administration of an anti-tuberculous agent, the cavity and infiltration were enlarged on a chest X-ray and the patient died due to respiratory failure. Cases of tuberculosis resulting in death after a short duration of infliximab treatment have been rarely reported. We speculate that chest CT and the interferon-gamma release assay (IGRA) for tuberculosis screening should be evaluated before starting infliximab treatment, and preventive administration of isoniazid should be considered with consultation with a pulmonologist.

Keywords: Pulmonary tuberculosis; Infliximab; Rheumatoid arthritis

Introduction

Tuberculosis remains one of the major causes of death worldwide [1]. The World Health Organization (WHO) estimated that 8.6 million people developed tuberculosis and 1.3 million died from the disease in 2012 [2]. In Japan, the incidence of tuberculosis was reduced to 20 per 100,000 persons in 2007 and continued to decline, reaching 16.1 in 2013. However, 20,495 newly notified tuberculosis patients existed in 2013, and the proportion of elderly people infected has increased [3].

Rheumatoid arthritis (RA) patients often have complicated infection, including tuberculosis, due to the use of adrenocortical steroids, and immunosuppressive agents. The use of an immunosuppressive agent is one of the risk factors of tuberculosis as well as a gastric ulcer, renal failure, pneumoconiosis, cancer and infection with human immunodeficiency virus [4-6]. When receiving treatment with an immunosuppressive agent, the relative risk of complication with tuberculosis in RA patients was 11.9 times compared with healthy subjects [4].

Tumor necrosis factor-alpha (TNF-α) is a cytokine involved in inflammation and joint destruction in RA patients. TNF-α also plays an important role in the prevention of infections such as tuberculosis. Infliximab is an antagonist of TNF-α and one of the biological agents used for the treatment of rheumatoid arthritis, Crohn's disease, psoriasis vulgaris, and Behcet's disease. While infliximab has been demonstrated to reduce the symptoms of these diseases, it can lead to an increased risk of infection. A previous study showed that in 5,000 RA patients treated with infliximab in Japan, 108 patients (2.2%) developed bacterial pneumonia, 22 patients (0.4%) developed pneumocystis pneumonia, and 14 patients (0.3%) developed tuberculosis [7].

We herein report the case of a 72-year-old Japanese woman with RA who developed tuberculosis after a month of starting infliximab treatment and died within a month after admission.
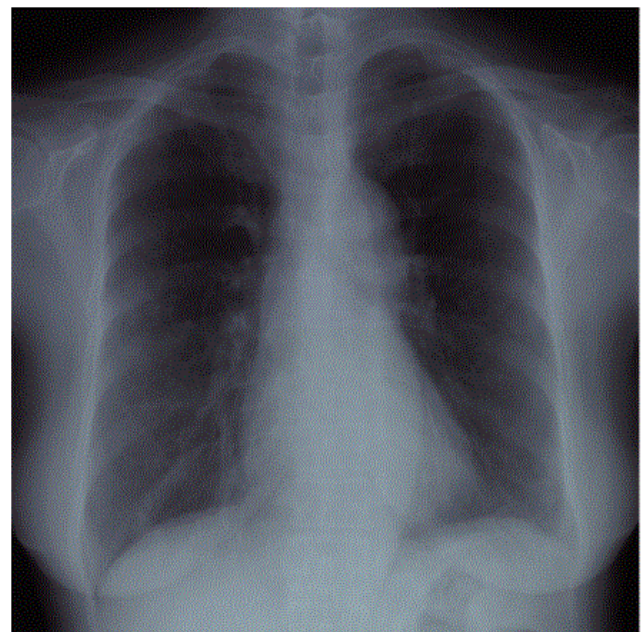

Figure 1: A chest X-ray obtained before infliximab treatment. No abnormal shadows were detected.

Case Report

A 72-year-old Japanese woman had seen a local doctor for RA, diabetes mellitus, hypothyroidism and hypertension. She did not have a history of tuberculosis. For RA pain of the left wrist, middle finger, and ring finger, the patient had been taken bucillamine since June 2008. Due to a rash on both lower legs, her treatment was changed from bucillamine to azathioprine and prednisolone (PSL) 5 mg/day in September 2008. In April 2010, due to worsening of arthralgia, the patient's treatment was changed to etanercept 25 mg/week, PSL 5 mg/day, and methotrexate 8 mg/week. At that point, a tuberculin skin test was positive. The patient's condition was improving, thus PSL was gradually tapered and discontinued on March 1, 2012 and etanercept and methotrexate were continued. After recurrence of arthralgia, her treatment was changed from etanercept to infliximab and PSL. She was administered Infliximab 174 mg/body (3 mg/kg) and PSL 10 mg/day was started on April 5, 2012, and methotrexate 8 mg/week was continued. A chest X-ray showed no abnormal shadows (Figure 1). She was administered infliximab 174 mg/body (3 mg/kg) as 2nd time administration on April 19, 2012.

On April 29, 2012, the patient was admitted to the emergency department with a half-month history of a fever, fatigue, dyspnea, and cough and a 2-day history of anorexia and nausea. A chest X-ray at this time revealed an infiltrative shadow with a cavity in both upper lobes. She received antibacterial therapy of meropenem and minomycin for bacterial pneumonia. The night of the same day, a smear for acid-fast bacilli obtained from the patient's sputum was positive (Gaffky 5), and a polymerase chain reaction (PCR) analysis for tuberculosis was positive. The patient was diagnosed with pulmonary tuberculosis and transferred to our hospital on May 1, 2012.
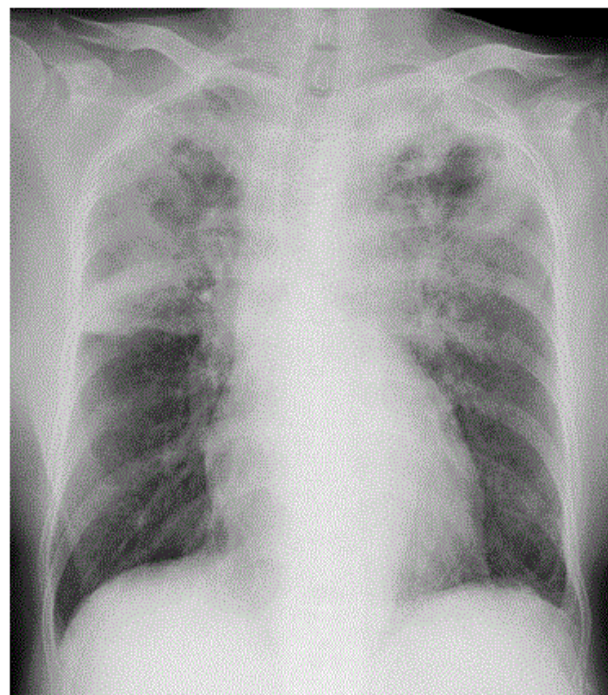

Figure 2A: A chest X-ray obtained on admission. The chest X-ray showed infiltration with a cavity in both the upper to middle lung fields.

Hematology		Biochemistry	
WBC	11,000 /μl	Alb	2.1 g/dl
RBC	402×10^4 /μl	AST	30 IU/L
Hb	12.3 g/dl	ALT	20 IU/L
Plt	20.8×10^4 /μl	LDH	334 IU/L
Serology		ALP	253 IU/L
CRP	27.43 mg/dl	ChE	101 IU/L
Acid-fast Bacilli in sputum		γ-GTP	50 IU/L
Day 1 smear Gaffky 5,		T.Bil	2.1 mg/dl
PCR of tuberculosis (+), culture (+)		Amy	46 IU/L
Day 2 smear Gaffky 6,		BUN	15.1 mg/dl
PCR of tuberculosis (+), culture (+)		Cr	0.53 mg/dl
		Na	122 mg/dl
		K	3.9 mg/dl
		Cl	86 mg/dl
		Glu	141 mg/dl

Table 1: Laboratory data. PCR: Polymerase Chain Reaction.

The patient's temperature was 38.2, pulse rate was 80/min, and blood pressure was 130/70 mmHg on this admission. She had respiratory failure; she was started on oxygen therapy (1 L/min O_2 through a nasal cannula). The patient's laboratory data showed a high white blood cell count and high C-reactive protein level (Table 1). There was a prominent infiltrative shadow with a cavity in both upper fields on admission (Figure 2A). Chest CT demonstrated that there were infiltrative shadows with a massive cavity in both upper lobes in a comparatively broad area, and random patchy and nodular shadows in both lung fields (Figure 2B). We discontinued infliximab treatment and started treatment with isoniazid (300 mg/day), rifampicin (450 mg/day), ethambutol (750 mg/day), and pyrazinamide (1.2 g/day). Due to the possibility of a lung abscess, we also administered sulbactam/ampicillin 4.5 g/day. After the initiation of therapy, she continued to have a high fever, fatigue, and anorexia. Additionally, the X-ray showed that the infiltrative shadow in both upper lobes was enlarged and patchy and nodular shadows appeared in the middle and lower fields (Figure 3). The patient's respiratory failure subsequently progressed. We speculated initial aggravation after the treatment of an antituberculous agent, and administered methylprednisolone 1,000 mg/day for three days. Despite the treatment of antituberculous agents, antibiotics, and a steroid, the patient's general condition worsened and she died due to respiratory failure on day 27. An autopsy was not permitted.

Discussion

We herein reported a case of RA who developed tuberculosis after infliximab treatment. Infliximab is antagonist of TNF-α and has been used for the treatment of RA, Crohn's disease, psoriasis vulgaris, and

Behcet's disease. This agent has been demonstrated to reduce the symptoms of such diseases, although it can lead to an increased incidence of infections, including mycobacterium infection.
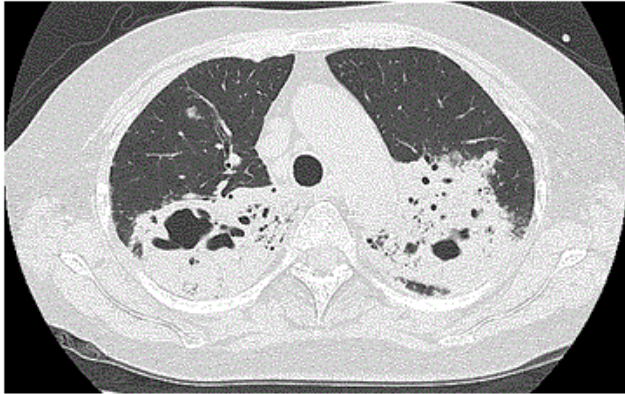

Figure 2B: Chest computed tomography (CT) performed on admission. CT showed widespread consolidation with a cavity in both upper lobes.
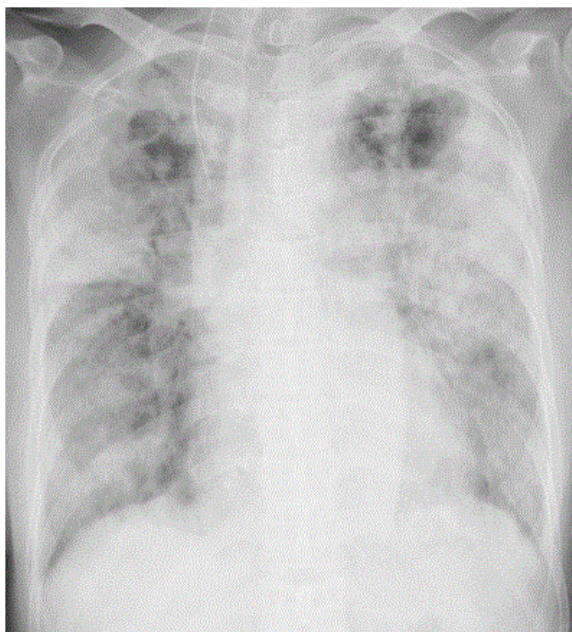

Figure 3: A chest X-ray obtained after half-month from admission. The X-ray showed that the infiltrative shadow in both upper lobes was enlarged and patchy and nodular shadows appeared in the middle and lower fields.

It has been reported that TNF-α plays an important role in preventing mycobacterium infection. Alveolar macrophages that phagocytose Mycobacterium tuberculosis produce TNF-α, interleukin-12 and other cytokines and activate CD4-positive T-cells. Interferon-γ produced by CD4-positive T-cells has been shown to induce the apoptosis of macrophages that have phagocytosed *M. tuberculosis*, thus leading to the formation of a granuloma and a

recovery from tuberculosis infection. Infliximab has been demonstrated to control the function of TNF-α and inhibit the formation of a granuloma, thus increasing the complication of infections such as tuberculosis. Therefore it is important to evaluate the risk of infections before the treatment of a biological agent including infliximab. In mycobacterial infection, risk factors for the complication of tuberculosis include a past history and family history of tuberculosis, findings of old tuberculosis on a chest X-ray or CT, strongly positive results in tuberculin skin test, and a positive results according to an interferon-gamma release test (IGRA) such as QuantiFERON-TB (QFT). Thus we should perform screening tests such as a medical examination by interview, a chest X-ray (or CT), sputum culture, tuberculin skin test, and the IGRA before administering infliximab. Most Japanese people received the Bacillus Calmette-Guerin (BCG) vaccine for tuberculosis in childhood, and thus are frequently positive for the tuberculin reaction. However, the IGRA is not influenced by previous BCG vaccination; therefore, we speculate that the IGRA has a superior ability of screening for tuberculosis than the tuberculin skin test in Japan. We previously reported a case of pediatric pulmonary tuberculoma that a chest X-ray failed to detect, but chest CT revealed. QFT positive patients with respiratory symptoms or frequent contact with infected individuals are recommended to undergo chest CT even if a chest X-ray did not show any abnormal shadows [8].

The RA guidelines in Japan recommend a chest X-ray and the IGRA or tuberculin test as screening tests for tuberculosis before starting treatment with biological agents. When active tuberculosis is confirmed, then we must perform standard therapy for tuberculosis. If latent tuberculosis infection is confirmed, then isoniazid should be administered for six or nine months. In the present case, there were no abnormal shadows in the chest X-ray, but positive in the tuberculin test before starting treatment of infliximab, so IGRA and chest CT should be confirmed.

Post marketing surveillance showed that in 5,000 RA patients treated with infliximab in Japan, 14 patients (0.3%) developed tuberculosis: 12 recovered by anti-tuberculosis therapy and 2 died due to causes other than tuberculosis [7]. Additionally, Kanae et al. previously reported that the median interval from the start of infliximab treatment until the development of tuberculosis was 12 weeks (range 1 to 52) and its peak was around 6-8 weeks [9]. However, it is rare that the present case developed tuberculosis after almost 4 weeks of infliximab treatment and thereafter died within one month after admission. We thought that the treatment with prednisolone, methotrexate, and etanercept for RA before starting infliximab might lead to a reduction of cell-mediated immunity, thus the interval from the start of infliximab treatment to the development of tuberculosis was shortened, and the condition of the present case worsened. Our findings suggest that the screening and prevention of tuberculosis should be carefully conducted, especially when considering a change in the therapeutic agents with infliximab for RA.

Furthermore, some of the clinical features of tuberculosis after infliximab treatment differ from general tuberculosis. In general, pulmonary tuberculosis accounts for 90% of all tuberculosis, however, extrapulmonary tuberculosis and miliary tuberculosis are relatively frequently observed in tuberculosis following infliximab treatment. Huang et al. reported that lymphadenopathy, pleural effusion, and pericardial effusion in the chest X-ray findings were more common in tuberculosis following anti-TNF-α therapy than without it [10].

It has been discussed that clinicians should discontinue treatment with TNF-α in patients who develop tuberculosis. Conversely, because the discontinuation of biological agents can lead to the exacerbation of RA and tuberculosis, a complicated paradoxical reaction, it was recently reported that clinicians should continue treatment with biological agents in patients who develop tuberculosis. There were some reports of complicated paradoxical reaction cases. In these reports, RA patients with complicated tuberculosis received the anti-tuberculous treatment and stopped biological agents, but patients' condition was worsened. After that resumed treatment with biological agents such as infliximab and adalimumab, their conditions were improved [11,12]. Wallis reported that the treatment of antituberculous agents with etanercept or a high dose of adrenocorticosteroid led to a greater acceleration of the conversion of sputum culture of tuberculosis than treatment with only antituberculous agents in tuberculosis patients [13]. Whether or not treatment with biological agents can be continued in patients who develop tuberculosis remains controversial, and a greater accumulation of cases is needed.

In conclusion, when administering infliximab therapy for RA, we should take account of the increased risk of infection. In tuberculosis infection, including latent tuberculosis infection, chest CT and the IGRA should be evaluated before starting infliximab treatment for RA, and continuous observation should be performed in collaboration with pulmonologists.

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