CASE REPORT

Pulmonary Infectious Complications Associated with Anti-TNFα Therapy (Infliximab) for Rheumatoid Arthritis

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Abstract

Two patients with rheumatoid arthritis (RA) that developed serious infectious complications following anti-TNFα therapy (infliximab) are reported. Patient 1 developed tuberculosis with high fever, refractory diarrhea and mediastinal lymphadenopathy. Trans-bronchial needle biopsy was useful to confirm the diagnosis. Patient 2 showed sudden onset of dyspnea with diffuse bilateral lung infiltration caused by *Pneumocystis jiroveci* pneumonia and the diagnosis was confirmed by broncho-alveolar lavage. Physicians should be alerted to infectious complications with atypical presentation and rapid progression in infliximab-treated patients. Invasive diagnostic procedures including fiber-optic bronchoscopy may be necessary early in the course for such cases.

Key words: infliximab, anti-TNFα therapy, rheumatoid arthritis, tuberculosis, *Pneumocystis jiroveci* (carinii) pneumonia, fiber-optic bronchoscopy

(Introduction)

Recently, significant progress has been made in the understanding of cellular and molecular pathways associated with autoimmune diseases including rheumatoid arthritis (RA) (1). This has led to the development of new specific therapeutic agents targeting pro-inflammatory cytokines such as tumor necrosis factor α (TNFα) or IL-1β. Infliximab is a chimeric monoclonal antibody that strongly binds to TNFα and neutralizes its biological activity by inhibiting binding to its receptors. Infliximab is now widely used for the treatment of refractory RA, Crohn’s disease (CD) or psoriasis with obvious clinical benefit. However, several studies have reported that anti-TNFα therapy is associated with a high risk of serious infectious complications such as bacterial infections, tuberculosis and fungal infections (1, 2). Post marketing surveillance in Japan has identified that 0.33 percent of RA patients receiving infliximab had developed tuberculosis (3). Keane et al have already reported that the reactivation of tuberculosis occurring among patients receiving infliximab may show an unusual clinical manifestation (4). In such cases, it is sometimes difficult to make a final diagnosis only by using ordinary methods such as sputum or bone marrow aspiration. *Pneumocystis jiroveci* pneumonia has been well documented as an opportunistic infection associated with long-term usage of immunosuppressive agents or immunocompromised hosts such as patients with acquired immunodeficiency syndrome or cancer patients. Several cases with pneumocystis infection thus far have been reported after infliximab treatment for Crohn’s disease (5, 6). However, few cases have been reported with this complication among RA patients receiving anti-TNFα therapy (7). As pneumocystis pneumonia is a disease associated with rapid deterioration and high mortality, it is very important for physicians to be aware of this serious complication related to anti-TNFα therapy. Here, we report two cases with serious pulmonary infectious complication following infliximab treatment for RA, a case of tuberculosis with atypical clinical presentation and a case of *Pneumocystis jiroveci* pneumonia.

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Case Report

Case 1

A 66-year-old housewife with moderate RA presented with a 1-month history of fever and diarrhea. Nine years before admission, she was diagnosed with RA. She had previously received treatment with methotrexate (MTX) (12 mg/week), nonsteroidal anti-inflammatory drugs (NSAIDs) and corticosteroids in combination since December 2003. Four months before admission (August 26, 2004), the therapy had become insufficient to control her symptoms, and infusion of infliximab (3 mg/kg) was started under continuing usage of MTX (8 mg/week). Her PPD before infliximab administration was negative. No infusion reaction was observed. On November 20, 2004 (six weeks after the third infusion), she developed fever of 39°C, anorexia, diarrhea and general malaise. She had no history of pulmonary infectious diseases including tuberculosis, and her initial laboratory studies were unremarkable except for moderately increased CRP. Despite antibiotics treatment in the out-patient clinic, her symptoms did not improve. On admission (December 22, 2004), she had a temperature of 38°C, a pulse of 60 beats per minute, blood pressure of 124/70 mmHg, respiratory rate of 16 breaths per minute and an oxygen saturation of 98% while breathing room air. The physical examination was normal except for moderate bilateral lower extremity pitting edema. Laboratory tests showed leukocytosis (10,300 /mm³), elevated level of CRP (12.4 mg/dl), elevated erythrocyte sediment rate (44.3 mm/hr) and low serum albumin (2.0 g/dl). Her chest radiograph and CT demonstrated bilateral pleural effusion and remarkable bilateral hilar and mediastinal lymphadenopathy (Fig. 1). It also revealed small nodular opacities less than 3 mm in diameter in her right middle and lower lobes but no infiltration nor consolidation in the other lung fields. Again, her PPD test was negative. Her blood culture and sputum culture were negative and urinalysis and bone marrow aspiration were normal. On the sixth hospital day, trans-bronchial needle aspiration biopsy of a sub-carinal lymph node (#7) with a fiber-optic bronchoscope (Olympus BF 1T-240) was performed. The pathological findings of the biopsy specimen showed caseous necrotizing granulomas. In addition, Ziehl-Neelsen stain of the necrotizing tissue demonstrated acid-fast bacilli (Fig. 2). Polymerase chain reaction confirmed infection with the Mycobacterium tuberculosis. The trans-bronchial lung biopsy specimen obtained from peripheral lung contained no specific lesion for tuberculosis. Immediately after confirmation of the diagnosis, anti-tuberculosis chemotherapy (300 mg of isoniazid, 450 mg rifampicin, 750 mg ethambutol and 1,200 mg of pyrazinamide) was started. After two weeks of the therapy, all of her symptoms including fever, diarrhea, leg edema and general malaise completely disappeared. The hilar and mediastinal lymphadenopathy and bilateral pleural effusion on her CT also disappeared three months after initiation of the therapy.

Case 2

A 69-year-old housewife with a five-year history of RA started infliximab (3 mg/kg) with MTX therapy (8 mg/week) because of progressive symptoms on September 28, 2004. She had been treated with NSAIDs, disease-modifying anti-rheumatic drugs (DMARDs) and MTX (8 mg/week) since November 2003. She had diabetes mellitus for twenty years and received diet therapy with insulin administration. She had no history of infectious diseases. On November 30, 2004 (three weeks after the third infusion), she developed progressive exertional dyspnea and fever. On admission (De-
that anti-TNF therapy including infliximab administration is associated with some risks including a high rate of serious infectious complications, congestive heart failure, demyelinating diseases and systemic lupus erythematosus (1). Among them, the increased risk of tuberculosis reactivation is especially important in Japan because Japan still has a higher endemic rate of tuberculosis than other industrialized countries. It was reported that the estimated rate of tuberculosis among patients receiving infliximab in the United States was 24.4 per 100,000 per year whereas the background rate is 6.2 per 100,000 per year (4). In Japan, the background rate is about four times higher than in the U.S. (24.8 per 100,000 per year). Thus, the rate of tuberculosis among patients who are treated with anti-TNFα agents would be much higher. According to post-marketing surveillance in Japan, 13 cases of tuberculosis have been reported among 4,000 patients with administration of infliximab (3). As most cases are thought to be reactivation of latent tuberculosis, physicians should be more alert in detecting for latent tuberculosis in such highly endemic countries like Japan. However, cases with no apparent past history of tuberculosis like the one under study here (case 1) may develop active tuberculosis. Importantly, as many people have had BCG administration in Japan, a PPD test can not have much informative impact. Recently, the Japanese Society for Tuberculosis and Japan College of Rheumatology have proposed guidelines for the selection of patients with a high risk of reactivation of tuberculosis after immunosuppressive therapy and recommend more active anti-tuberculosis therapy (8). Adequate production of TNFα is thought to be essential for protective immunity against tuberculosis including granuloma formation and inhibition of dissemination (9). Thus, patients with tuberculosis who lack adequate TNFα production show more disseminated, rapid and unusual presentation. In such unusual cases, early diagnosis is sometimes very difficult, and delay of the initiation of therapy would further worsen the outcome. Therefore, considering the appropriate approach to the diagnosis of tuberculosis occurring after anti-TNFα therapy is very important. It is well known that many cases with tuberculosis after anti-TNFα therapy have extra-pulmonary diseases and show atypical presentations (3). In the present patient (case 1), bacteriological examination of sputum, urine and bone marrow aspiration showed no abnormal findings. She showed mediastinal lymphadenopathy as a dominant finding. Thus, we performed trans-bronchial needle aspiration biopsies early in the course, which led to the final diagnosis. Gleeson et al reported that needle biopsy of mediastinal lymph nodes was beneficial for diagnosis of a case with tuberculosis after infliximab administration (10).

**Pneumocystis jiroveci** pneumonia is well known to be associated with various immuno-compromised conditions such as human immunodeficiency virus (HIV) infection or prolonged administration of immunosuppressive agents. Although few cases have been reported in the literature, post-marketing surveillance in Japan revealed that the incidence rate of pneumocystis pneumonia after infliximab administration was 0.38% (15/4000) (11). Although the surveillance includes clinically suspected cases of pneumocystis pneumonia, the rate of the disease is higher than that of tuberculosis related to infliximab (0.33%) (3). In Japan, infliximab infusion accompanied by low-dose administration of MTX is recommended for treatment of RA patients. The combination of infliximab and MTX is thought to be beneficial for preventing production of human anti-chimera antibody (12).
Krebs and Gibbons reported that low dose MTX could be a risk factor for developing pneumocystis pneumonia (13). As far as we investigated, there have been four case reports on pneumocystis pneumonia after infliximab administration (5-7, 14). Three of those were patients with Crohn’s disease and received both azathioprine and infliximab. Thus, physicians should be more aware of this severe infectious complication in patients receiving infliximab-treated patients, and adequate therapy must be initiated promptly. In our second case, we performed bronchoalveolar lavage immediately after diffuse lung infiltration appeared, allowing us to make the final diagnosis and initiate treatment rapidly. These facts suggest that one must be more on the alert of infectious complications in RA patients receiving infliximab (with MTX) and a more aggressive approach for diagnosis should be considered early in the course.

In summary, we reported two cases treated with infliximab that had developed serious pulmonary infectious complications. As infliximab efficiently suppresses TNFα-mediated immunity and is administered in combination with MTX, clinicians always should be aware of the risk of various severe infectious complications. In such cases, early invasive diagnostic procedures including trans-bronchial needle aspiration (TBNA) or BAL using fiber-optic bronchoscope may be useful to determine diagnoses immediately and prevent delay in starting adequate therapies.

References


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