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□ Case Report □

A Case of Invasive Pulmonary Aspergillosis in a Patient with Rheumatoid Arthritis Treated with Adalimumab

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We describe a fatal case of invasive pulmonary aspergillosis in a patient with rheumatoid arthritis receiving the TNF-α inhibitor, adalimumab. The use of TNF-α inhibitor has been associated with an increased risk of infections, including tuberculosis and other opportunistic infections. Physicians should have a high index of suspicion for opportunistic infection that can develop during TNF-α inhibitor treatment.

***Key Words*. Invasive aspergillosis, Rheumatoid arthritis, Tumor necrosis factor-alpha**

Introduction

Rheumatoid arthritis (RA) is an autoimmune inflammatory disease. It has been recognized that an excessive production of the inflammatory cytokines such as, tumor necrosis factor alpha (TNF-α) cause synovitis and joint destruction (1). Currently, three kinds of TNF-α inhibitors have been used for the treatment of RA: infliximab, etanercept, and adalimumab. These agents are reducing inflammatory disease activity and slowing radiographic progression (2,3). TNF-α is not only a major mediator of inflammation but also an integral part of normal defense response against infection. It is involved in apoptosis, cell activation, induction of other inflammatory cytokines, and recruitment of inflammatory cells to site of infection (1). Patients treated with TNF-α inhibitor show a decreased production of interferon-γ and decreased expression of Toll-like receptor-4 (TLR-4), which is necessary for the recognition of microorganisms by phagocytes and dendritic cells (2). Therefore, the use of TNF-α inhibitor is anticipated to increase susceptibility to bacterial or fungal pathogens (4,5). Both opportunistic and bacterial infections have been described. Few cases of fungal infections complicating such therapy have been reported in Korea (6-8).

We describe the development of invasive pulmonary aspergillosis in a patient with RA after treatment of TNF-α inhibitor, adalimumab. She died from progressive respiratory failure and septic shock despite of anti-fungal treatment and intensive care.

Case Report

A 66-year-old woman with seropositive RA presented with productive cough and malaise for 2 weeks. She had suffered from RA for 3 years with recurrent flares of polyarthritis involving hands, wrists, and knees. During the course of disease, she underwent trials of multiple different disease modifying anti-rheumatic drugs (DMARDs) including hydroxychloroquine, sulfasalazine, leflunomide, cyclosporine, and methotrexate with limited improvement. Two months earlier, adalimumab (40 mg subcutaneous every other week) was added to her medication of celecoxib (400 mg/day), prednisolone (7.5 mg/day), and methotrexate (15 mg/week) resulting in improvement of her symptoms. She had a negative tuberculin skin test and QuantiFERON®-TB test with normal chest radiographic finding at the time of initiation of adalimumab (Fig. 1).

On admission, her blood pressure was 150/90 mmHg, pulse 95/min, temperature 36.8°C and respiratory rate 24/min. Chest and abdominal examination were unremarkable. There was no evidence of exacerbation of arthritis. Laboratory tests revealed

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hemoglobin was 11.0 g/dL WBC 6,820/mm^3, platelet 216,000/mm^3, erythrocyte sedimentation rate 13 mm/hr and C-reactive protein 0.54 mg/dL. The blood urea nitrogen was 33.2 mg/dL, creatinine 1.18 mg/dL, total protein 7.0 g/dL, albumin 4.4 g/dL, AST 40 IU/L, ALT 28 IU/L, and alkaline phosphatase 77 IU/L. Rheumatoid factor was positive. Antinuclear antibody and antibody to cyclic citrullinated peptides (anti-CCP) were negative. Antibodies against syphilis, hepatitis B, hepatitis C, or human immunodeficiency virus were all negative. Arterial blood gas analysis on room air was pH 7.47, $PaCO_2$ 35.9 mmHg, PaO_2 78.2 mmHg, and $SatO_2$ 96.7%. Chest X-ray showed a nodule on left lower lung with mild cardiomagaly (Fig. 2A). Computed tomography (CT) of the chest revealed a 3×3 cm sized cavitated pulmonary nodule on left lower lobe with underlying bronchiectasis (Fig. 2B). It was highly suggestive of a fungus ball, aspergilloma. Sputum cultures for bacteria, fungi, and mycobacteria were negative. Percutaneous fine needle aspiration of the lung nodule revealed numerous septate hyphae branching at acute angles, morphologically consistent with aspergillus (Fig. 3). Adalimumab and methotrexate were discontinued and treatment with itraconazole (400 mg/day) was started. However, her symptoms deteriorated with intermittent fever and worsening dyspnea. Chest examination revealed coarse crackles on both lung fields. On the 12th day of admission, massive bilateral pulmonary infiltrates showed on chest X-ray (Fig. 4A). And repeated chest CT demonstrated newly developed extensive bilateral ground-glass opacifications (Fig. 4B). Because of an additional opportunistic pulmonary infection was suspected, bronchoscopy was performed. A bronchoscopy showed increased secretions without endobronchial lesion. Cultures of bronchoalveolar lavage fluid and lung nodule aspirates yielded

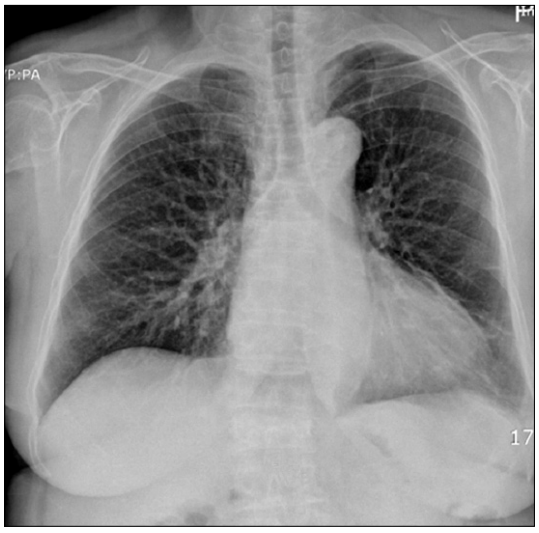

Figure 1. Chest radiograph shows no parenchymal lung lesion before the treatment of adalimumab.

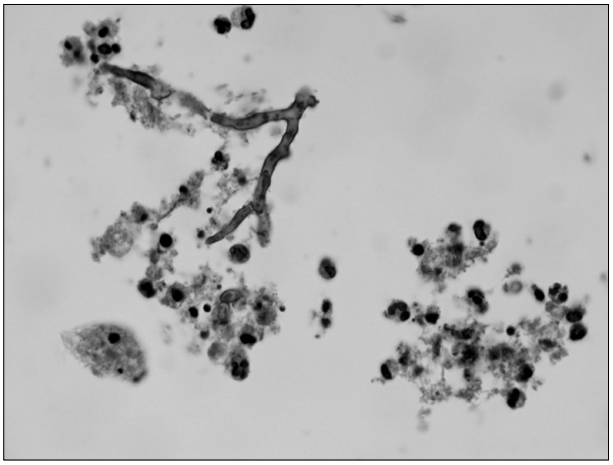

Figure 3. Microscopic examination of lung nodule aspirates shows thin septate hyphae branching at acute angles (H&E, ×400).

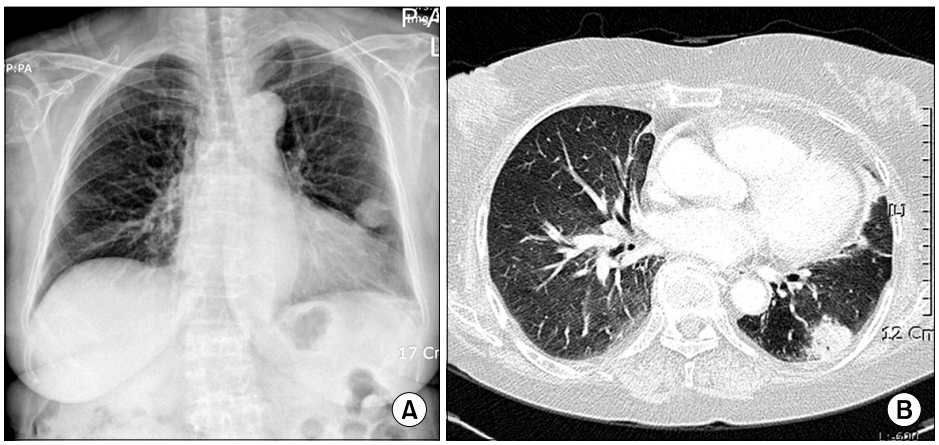

Figure 2. On admission, chest X-ray shows nodular shadow on the left lower lung field (A). Chest CT reveals a 3×3 cm sized nodule in the left lower lobe of the lung with underlying bronchiectasis (B).

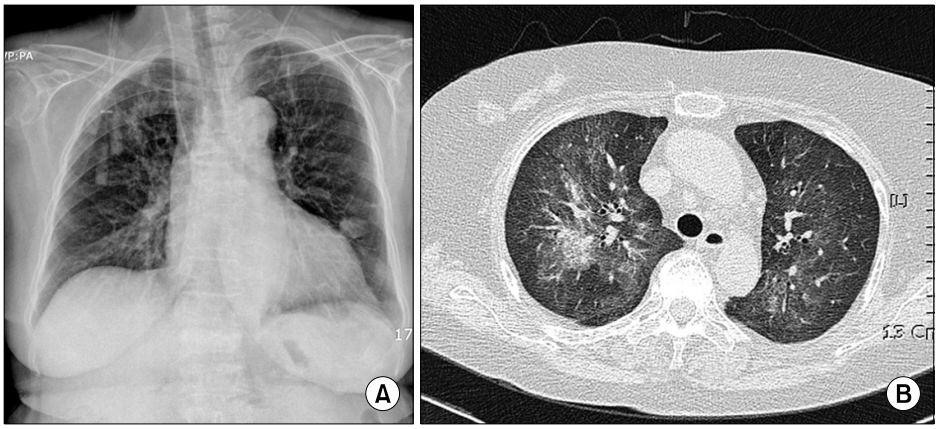

Figure 4. On the 12th day of admission, chest X-ray shows bilateral massive infiltrates (A). Chest CT shows diffuse ground-glass opacifications (B).

Aspergillus fumigatus. The analyses of galactomannan on repeated plasma samples were negative. Blood and sputum cultures for bacteria and fungi were negative at that time. The patient was treated with ceftriaxone, vancomycin, azithromycin, and voriconazole (400 mg/day). Despite the intensive treatment, acute deterioration followed with refractory hypoxia and hypotension. The patient died from progressive multiorgan failure and secondary bacterial septic shock on the 25th day of admission.

Discussion

The introduction of cytokine based therapy has improved the therapeutic options of several inflammatory diseases. Among them TNF-α inhibitor have revolutionized the treatment of RA, ankylosing spondylitis, psoriatic arthritis and Crohn's disease (1-3). Adalimumab is a recombinant human immunoglobulin monoclonal antibody that binds to the soluble and transmembrane form of TNF-α with high affinity, thereby preventing TNF-α interaction with its receptors. TNF-α inhibitors have been associated with an increased risk for infection, particularly by pathogens cleared by a granulomatous response (3). Reports of serious infections associated with use of TNF-α inhibitors have accumulated gradually during the past several years (1-3). Recent large registry studies showed the incidences of serious infections among the RA patients receiving etanercept of 6.4, infliximab of 6.2 and adalimumab of 5.5 cases per 100 patient-years respectively (9,10). The incidence of serious infections among the Korean RA patients treated with TNF-α inhibitors was significantly high compared with that of those patient treated with conventional DMARDs (8% vs 5.1%). And the most common infection site was respiratory tract (11). Upon review of the MEDLINE and PubMed database from January 1966 to June 2007, Tsiodras et al found that 281 cases of invasive fungal infections associated with TNF-α inhibitor, 80% were associated with infliximab, 16% with etanercept, and 4% with adalimumab. The common fungal pathogens were histoplasma, candida, and aspergillus. Among 64 cases of aspergillosis associated with TNF-α inhibitor, 75% were associated with infliximab, 22% with etanercept, and 3% with adalimumab (4). Because adalimumab had not been widely used at that period, few cases of adalimumab associated infections were noted. The number of infections can rise with widely use of adalimumab and longer follow-up. Fungal infections occurred a median of 55 days after initiation of infliximab and 144 days after the treatment of etanercept. Many infections occurred after 3 or fewer infusions, and thus the rate of fungal infections does not appear to correlate with the number of infusions, at least for infliximab (4). In a trial of adalimumab therapy for RA, risk factors for serious infection included old age, male, and comorbid conditions such as, cardiopulmonary disease (10). Besides of these factors, concomitant use of immunosuppressive agents, such as corticosteroids seems to be an additional role in development of infection.

TNF-α is a central mediator in inflammation and immunity. Specifically, TNF-α appears to have important roles in the formation and maintenance of granuloma, the migration and maturation of inflammatory cells to the site of infection, and the production of cytokines and adhesion molecules (1). TNF-α is also involved in maintaining a T-helper cell type 1 immune response, it induces production of fungicidal interferon-γ. Interferon γ is crucial for proper activation of phagocytosis and killing of intracellular pathogens. Pulmonary alveolar macrophages are a major defense against fungal invasion. TNF-α appears to enhance alveolar macrophage phagocytosis of fungus and oxygen production with subsequent hyphae damage by neutrophils (12).

Aspergillus is a saprophytic ubiquitous environmental fungus

capable of causing a wide variety of diseases in both healthy and immunocompromised persons. It is usually acquired by inhalation of airborne spores. Pulmonary aspergillosis presents different types depending on the host immune status: invasive aspergillosis, allergic bronchopulmonary aspergillosis, and aspergilloma. Invasive pulmonary aspergillosis occurs usually in the elderly person or immunocompromised host (12). Furthermore, TNF-α inhibitor may exacerbate latent fungal infections, causing an aspergilloma to progress to invasive aspergillosis, like this patient (12,13).

To prevent the reactivation of latent tuberculosis during TNF-α inhibitor therapy, patient should be screened for tuberculosis before therapy is initiated. The routine screening has reduced the occurrence of TNF-α inhibitor associated tuberculosis. Unlike tuberculosis, there are no guidelines on screening for other opportunistic infections. Because few cases of fungal infection in patients treated with TNF-α inhibitors have been reported, prophylactic treatment or routine screening is not recommended (14). Furthermore, infections in patients receiving TNF-α inhibitors may be severe and may mask signs of serious infection. If active infection is suspected in a patient who is receiving TNF-α inhibitor, the drug should be discontinued and should be treated appropriately. With this fatal case we would like to support the observations that the use of TNF-α inhibitors increases the risk of serious opportunistic infections by inhibition of a physiologic TNF-α response. To the best of our knowledge, this case represents the first case of invasive pulmonary aspergillosis associated with adalimumab in Korea.

In conclusion, careful monitoring is necessary to recognize the possible occurrence of opportunistic infections including invasive aspergillosis in patients treated with TNF-α inhibitors.

Summary

We describe a fatal case of invasive pulmonary aspergillosis in a patient with RA receiving TNF-α inhibitor, adalimumab. The use of TNF-α inhibitor has been associated with an increased risk of infection such as, tuberculosis and other opportunistic infections. Physicians should have a high index of suspicion for opportunistic infection that can develop during TNF-α inhibitor treatment.

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