Adalimumub-induced Interstitial Pneumonia with an Improvement of Pre-existing Rheumatoid Arthritis-associated Lung Involvement

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Abstract

A 78-year-old man with an 18-year history of rheumatoid arthritis (RA) was treated with tumor necrosis factor (TNF)-α inhibitor adalimumab. Chest computed tomography showed a previously detected consolidation. The patient’s arthritic symptoms substantially decreased with the initiation of adalimumab, with a simultaneous improvement of the lung lesion. However, additional interstitial pneumonia was found a month after starting adalimumab. This course suggested that adalimumab might be effective against RA-associated lung disease, but may also have caused drug-induced interstitial pneumonia. This is the first report indicating that TNF-α inhibitor shows simultaneously conflicting actions in a patient with RA-related lung disease.

Key words: adalimumab, rheumatoid arthritis, drug-induced interstitial pneumonia, tumor necrosis factor-α

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Introduction

Tumor necrosis factor (TNF)-α inhibitors have been increasingly used to treat rheumatoid arthritis (RA) due to their effectiveness and acceptable safety profiles. However, the adverse effects of TNF-α inhibitors include opportunistic infections, liver injury, and drug-associated interstitial lung disease. Several reports have so far described TNF-α inhibitors-induced interstitial pneumonia (1-5). On the other hand, a few reports have suggested that TNF-α inhibitors may be an important therapeutic strategy in the management of RA-associated lung disease (6). Adalimumab (HUMIRA, Abbott) is the third TNF-α inhibitor to be approved after infliximab and etanercept. This report presents a case of adalimumab-induced interstitial pneumonia, in which an improvement of pre-existing lung disease was simultaneously observed, in a patient with RA.

Case Report

A 78-year-old man was diagnosed with RA in 1992 based on the presence of polyarthritis, morning stiffness and the presence of rheumatoid factor. He had been consecutively treated with 5 mg/day prednisolone, non-steroidal anti-inflammatory drug, and disease modifying antirheumatic drugs (DMARDs), including methotrexate, bucillamine and sulfasalazine. Adalimumab (40 mg) was subcutaneously injected biweekly in December 2009, because his disease activity was not adequately controlled by the previous medications. Chest computed tomography (CT) showed no interstitial shadows, such as usual interstitial pneumonia (UIP) or non-specific interstitial pneumonia (NSIP) pattern prior to the administration of adalimumab, and there was a consolidation with an air-bronchogram in the right middle lobe (Fig. 1a), which had been previously detected at the time of the diagnosis of RA. However, his sputum culture was negative for pathological bacteria including Mycobacterium tuberculosis and nontuberculous mycobacteria, and the Quantiferon®-TB Gold (Cellestis, Ltd., Carnegie, Victoria, Australia) was negative, thus he was not given any prophylaxis against infections. At the initiation of adalimumab, the serum level of KL-6 as a marker of interstitial pneumonia was normal (492 U/mL), the anti-neutrophil cytoplasmic autoan-
Figure 1. a. Chest computed tomography (CT) before treatment with adalimumab showed consolidation with an air-bronchogram in the right middle lobe (arrows). b. Chest CT after the treatment of adalimumab showed diffuse ground-glass opacities with traction bronchiectasis in both lower lobes, and an improvement of the consolidation in the right middle lobe.

tibodies were negative, and there were no clinical findings of vasculitis. His arthritic symptoms were substantially improved after the initiation of adalimumab, and the counts of joint swelling and tender joints were reduced from 13 to 5, and 8 to 5, respectively. However, a month later, the patient began to complain of fever and a non-productive cough.

A physical examination revealed a slight swelling of the proximal interphalangeal joints of the hands and the wrist joints bilaterally. His body temperature was 37.2°C, blood pressure was 122/64 mmHg, and heart rate was 82/min. A chest examination showed fine crackles bilaterally. Laboratory findings included a normal leukocyte count (8,840/μL) without eosinophilia, slightly elevated transaminase (aspartate aminotransferase 50 IU/L, alanine aminotransaminase 49 IU/L), and a high level of C-reactive protein (9.65 mg/dL). The serum KL-6 level was elevated (3,399 U/mL), while the β-D-glucan level was within the normal range, and a PCR assay of his sputum for *Pneumocystis jiroveci* and a Cytomegalovirus antigenemia assay of his white blood cell were both negative. A rapid diagnosis kit for influenza virus, serum antibodies for *Mycoplasma pneumonia* and *Chlamydia pneumoniae* were all negative. The additional serological findings: IgM rheumatoid factor; 732 U/mL, anti-cyclic citrullinated antibodies; 73.0 U/mL, antinuclear antibody; 1 : 160, and the anti-neutrophil cytoplasmic autoantibodies were still negative. Respiratory function tests showed a vital capacity of 1.84 L (58.8% of predicted). High-resolution CT (HRCT) of the chest demonstrated an improvement of the consolidation in the right middle lobe and new diffuse ground-glass opacities with traction bronchiectasis in both lower lobes (Fig. 1b).

No bronchoscopy was performed due to the patient’s poor respiratory condition and a severe myocardial risk associated with his history of three vessel coronary artery disease. However, adalimumab-induced interstitial pneumonia was suspected rather than atypical pneumonia based on his clinical course, although the drug-induced lymphocyte stimulation test was negative. Therefore, adalimumab was discontinued and methylprednisolone pulse therapy followed by 30 mg/day of prednisolone was administered instead. The fever and non-productive cough gradually disappeared within a few days after the start of treatment with methylprednisolone. Prednisolone was tapered over the course of the following 2 weeks. HRCT showed an improvement in the bilateral ground-glass opacities one month later.

**Discussion**

There are several reports of interstitial pneumonia induced by TNF-α inhibitors such as infliximab, etanercept and adalimumab (1-5, 7, 8), and four cases of adalimumab-induced interstitial pneumonia have been re-
ported (1, 2, 5, 7). The periods from the initiation of adalimumab administration to the onset of interstitial pneumonia were 2.5 months (7), 3 months (2), 5 months (5) and 3.5 years (1), respectively. Chest CT revealed bilateral ground-glass opacities with traction bronchiectasis in all cases, thus indicating the NSIP pattern in the CT classification of drug-induced interstitial pneumonia (9). The present case showed similar clinical features (1, 2, 5, 7), with the exception of the course of radiographic findings. The course of radiographic findings suggested that the infiltrate in the right middle lobe might be RA-associated lung disease because this shadow had been detected before TNF-α inhibitor treatment and diminished in response to this treatment, and that interstitial pneumonia was probably caused by adalimumab.

TNF-α inhibitors are also reported to be effective against RA-associated interstitial pneumonia (6). The radiographic pattern in this previous report might be that of UIP (6); however, the radiographic pattern of the pre-existing lesion of the present case was thought to be an organizing pneumonia (OP) pattern rather than a UIP or NSIP pattern. OP is a commonly-observed pattern in RA-associated interstitial pneumonia following UIP and NSIP patterns (10). These findings may suggest that the OP-like shadow in the right middle lobe, which had remained unchanged for several years, was improved by the administration of adalimumab in the present case. However, if this OP-like shadow was actually another pulmonary disorder, such as post-inflammatory scarring, it remains unclear whether or not the administration of adalimumab would be effective against such a pathological condition.

Anti TNF-α agents are reported to have the opposite efficacy: causing interstitial pneumonia, or inhibiting pulmonary inflammation/fibrosis, that probably depends on a different pathological condition (11, 12). Some authors have reported pre-existing lung disease in patients with RA to be a predictive factor for drug-induced pneumonitis (13, 14). Therefore, this risk factor may be overestimated and we may unfortunately rule out the chances to cure RA-associated lung disease in response to TNF-α inhibitor treatment. Dixon et al investigated the influence of anti TNF-α therapy on mortality in patients with pre-existing RA-associated lung disease (15). They concluded that the mortality in patients with RA-associated interstitial pneumonia was not increased following treatment with TNF-α inhibitors, in comparison to that with traditional DMARDs. However, there might be selection and reporting bias in this report, since this was an observational study and did not describe the radiographic and pathologic pattern of each RA-associated lung disease. Therefore, it is still difficult to determine the role of TNF-α inhibitor in RA-associated lung disease only based on the results of this study (15).

Interstitial pneumonia occasionally becomes a life-threatening adverse event during the treatment of RA. The use of TNF-α inhibitors can be associated with interstitial pneumonia. Therefore, clinicians must be aware of RA-associated or drug-induced interstitial pneumonia, as well as infections. In addition, prospective large studies are required to investigate the use of TNF-α inhibitors for RA patients with pulmonary involvement, and these studies should include various types of radiographic and pathological findings of the lung.

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

References


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