CASE REPORT

Mycobacterium abscessus Pulmonary Infection under Treatment with Tocilizumab

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Abstract

Although biological agents are of considerable benefit to patients with rheumatoid arthritis (RA), the potential for opportunistic infections is a critical issue. It is therefore important to achieve a balance between treatment efficacy and controlling opportunistic infection. We herein report the successfully managed case of a 53-year-old patient with RA who developed pulmonary Mycobacterium abscessus infection during treatment with tocilizumab and methotrexate.

Key words: Mycobacterium abscessus, non-tuberculous mycobacterium, opportunistic infection, rheumatoid arthritis

Introduction

Rheumatoid arthritis (RA) is a systemic inflammatory disease characterized by inflammation of the synovium and the breakdown of bone and cartilage in the joints, leading to functional disability. Biological disease-modifying antirheumatic drugs (DMARDs) are of considerable benefit in preventing joint destruction in RA patients, although the administration of these agents increases the possibility of opportunistic infection involving non-tuberculosis mycobacterium (NTM) (1, 2). In North America, the crude incidence of NTM per 100,000 patient-years in the general population, RA patients treated without tumor necrosis factor (TNF) antagonists and RA patients treated with TNF antagonists is reported to be 4.1, 19.2 and 105, respectively (3). NTM infection is of particular concern in patients with RA, particularly those who use biological DMARDs, and is regarded as a contraindication to the use of these medications in principle, although discontinuing these drugs inevitably results in flare-ups of the RA activity.

One previous study reported a death rate of 9% in patients using TNF antagonists who developed NTM infection (4). Among these patients, 12% had Mycobacterium abscessus infection. M. abscessus is the third most frequently recovered NTM respiratory pathogen in the United States, whereas it is rarely responsible for NTM respiratory infection in Japan (5). This microbe is a rapidly growing mycobacteria (RGM) and causes severe pulmonary infection resistant to conventional antibiotics and anti-tuberculosis agents. Although this bacterium is susceptible to clarithromycin (CAM), amikacin (AMK), cefoxitin (CXT) and imipenem/cilastatin (IPM/CS), no effective drug regimens have been firmly established (6). The prognosis of M. abscessus pulmonary infection is poor, with a reported mortality rate of 16-20% (7, 8). Relapse after remission is also frequent, and providing successful treatment for M. abscessus pulmonary infection is considered to be difficult.

We herein report a case of M. abscessus pulmonary infection associated with the use of tocilizumab (TCZ) and methotrexate (MTX). The infection was successfully controlled and the RA disease activity was managed with iguratimod (IGU) and salazosulfapyridine (SASP), despite the need to discontinue treatment with TCZ and MTX.

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**Case Report**

A 53-year-old Japanese woman complained of a mild productive cough occasionally associated with hemoptysis at a regular hospital visit in August 2013. Her symptoms had developed over the course of one week. She had a history of gastroesophageal reflux disease and had been treated for RA for 17 years. She had also undergone surgery several times for bone destruction due to poor disease control. She had previously received many DMARDs, including auranofin, bucillamine, D-penicillamine, mizoribine, MTX and adalimumab (ADA). Because her disease activity remained high despite the use of ADA, she was administered TCZ. In 2009, prior to the introduction of TCZ, bronchoscopy was performed to treat bilateral bronchiectasis and a nodular lung shadow suggestive of NTM infection. However, an examination of the bronchoalveolar fluid failed to demonstrate NTM. The patient was then treated with MTX at a dose of 8 mg/week and TCZ at a dose of 8 mg/kg/4 weeks without corticosteroids and finally achieved a low disease activity according to the Disease Activity Score in 28 joints based on the erythrocyte sedimentation rate (DAS28-ESR) (9).

The patient’s height was 164 cm and her body weight was 48 kg. Her body temperature was 36.5 degrees C, her blood pressure was 126/66 mmHg, her heart rate was 76 beats per minute and her respiratory rate was 12 breaths per minute. Coarse crackles were heard over the left lung. Deformities of the joints was evident in the bilateral wrists, knees and left elbow. Blood tests revealed a white blood cell count of 6,900/mm³, C-reactive protein concentration of 0.01 mg/dL and rheumatoid factor level of 154 IU/mL. Antiglycopeptidolipid (GPL) core antibodies were positive, suggesting NTM infection. A chest radiograph disclosed a small nodular lesion in the left lung that had not been evident in the scan obtained in April 2013. A computed tomography scan of the chest confirmed focal infiltration with bronchiectasis (Figure a, d, g), again suggesting NTM infection. The patient rarely experienced respiratory symptoms, and we did not detect any signs of active infection on routine radiographic and laboratory examinations conducted previously. We subsequently withdrew the dose of TCZ immediately; nevertheless, bronchoscopy with bronchoalveolar lavage was performed, and *M. abscessus* was identified on DNA-DNA hybridization (DDH Mycobacteria; Kyokuto, Tokyo, Japan).

Because the patient’s symptoms did not improve, and lung infiltration progressed in October 2013 (Figure b, e, h), a regimen consisting of CAM (800 mg, per os), AMK (15 mg/kg/ div) and IPM/CS (1.5 g/day div) was started and continued for one month then switched to CAM (800 mg, per os) and levofloxacin (500 mg, per os). Although her symptoms and radiographic findings gradually improved (Figure c, f, i), the discontinuation of TCZ, and later MTX, caused worsening of the RA disease activity. In particular, the Clinical Disease Activity Index (CDAI) (10) increased from 8.5 to 14, the DAS28-ESR increased from 1.89 to 4.26 and the serum matrix metalloprotease-3 level increased from 48.2 to 207.6 ng/mL. Igraturimod (IGU) was administered orally at a dose of 25 mg/day for the first four weeks followed by 50 mg/day, and the disease activity was successfully suppressed in combination with SASP therapy. In June 2014, the patient’s CDAI was 8.6, and her cough and hemoptysis had disappeared.

**Discussion**

Although *M. abscessus* pulmonary infection can be a life-threatening complication in patients with RA, only four such cases have been reported [(11-14) (Table)]. These RA patients included two individuals who had been treated with TNF antagonists (11, 12) and two who had not been treated with biological DMARDs (13, 14). Two of these four cases were fatal (11, 13). Because the mortality rate of *M. abscessus* infection is reported to be 16-20% (7, 8), clinicians must aware of its potential development in RA patients.

It has been reported that the onset of pulmonary NTM disease in RA patients appears to spread from pre-existing lung lesions, such as those involving bronchiectasis or nodules (12). However, it is currently unclear whether these pre-existing abnormalities reflect the subclinical presence of pulmonary NTM colonization or constitute an extra-articular manifestation of RA. The present patient developed NTM infection four years after being started on TCZ therapy. She had both nodular lesions and bronchiectasis, and bronchoscopy performed prior to the initiation of TCZ treatment showed no signs of any pathogens. Therefore, the patient appears to have developed an exogenous NTM infection, rather than endogenous reactivation. In cases of exogenous NTM infection, obtaining a timely diagnosis of pulmonary NTM disease is critical.

We were able to control our patient’s infection successfully. First, we effectively identified the pathogen in an expeditious manner and promptly started adequate treatment. *M. abscessus* pulmonary infection is critical and sometimes fatal due to its rapid exacerbation and resistance to ethambutol (EB) and rifampicin (RFP), which are usually employed for other NTM infections (6, 7). Because CAM monotherapy rapidly leads to acquired resistance and treatment failure, the use of a multi-drug regimen including CAM with AMK plus CXT or IPM/CS is recommended (5, 6). Mori et al. also highlighted the importance of early isolation and identification of the causative NTM species in cases of *M. abscessus* infection (14). Recently, testing for anti-GPL-core antibodies has become commercially available. This useful serologic test can be used to differentiate RA with *M. avium* complex (MAC) from RA without MAC, with a sensitivity of 100% and specificity of 90% (15). However, caution is required when interpreting the results. As RGM including *M. abscessus* has GPL-core antigens, positivity on this test
may also indicate the presence of RGM infection. In the present case, polymerase chain reaction (PCR) for *M. avium* and *M. intracellulare* yielded a negative result, while DDH demonstrated *M. abscessus* infection. Second, the patient’s underlying lung structure was relatively normal, apart from mild bronchiectasis. Cases of treatment-resistant NTM are sometimes associated with cavity formation, gastroesophageal disorders and/or cystic fibrosis (6, 7, 11, 13, 16, 17). Third, our patient had no history of CAM usage. Macrolide resistance in the setting of NTM is thought to result from previous exposure to antibiotics (18). Therefore, clinical isolates are believed to be sensitive to CAM, the anchor drug for the treatment of *M. abscessus* infection. Sensitivity tests for the isolated pathogen were not performed in the present case because this technique requires a special culture medium and the drug sensitivity of *M. abscessus* in the lungs did not reflect the need for this test *in vitro*. Finally, the speedy withdrawal of TCZ may have contributed to the patient’s favorable outcome via the resolution of immune insufficiency. Recently, a species closely related to *M. abscessus*, *M. massiliense*, has been described (19, 20). *M. massiliense* displays a lower frequency of acquired resistance to macrolides, and patients with pulmonary *M. massiliense* infection exhibit a milder clinical course than those with *M. abscessus* pulmonary infection (21, 22). Because *M. massiliense* cannot be distinguished from *M. abscessus* using traditional methods (23), there is a possibility that the infection in our patient may have been caused by *M. massiliense*. The development of a convenient phenotyping method and treatment regimens tailored to each species is desirable in the fu-

Figure. High-resolution computed tomography (HRCT) imaging. HRCT performed in August 2013 (a, d, g) revealed mild bronchiectasis in the left lung (a) with small centrilobular nodules in both lungs (a, g). An HRCT scan performed in October 2013 showed new infiltrates in the left upper and lower lobes (b, e, h). An HRCT scan performed after four weeks of treatment with intravenous imipenem/cilastatin and amikacin and oral clarithromycin showed that the abnormal findings had improved (c, f, i).
nature.

In this case, the discontinuation of TCZ and MTX resulted in an RA flare-up. MTX and biological DMARDs are effective in treating RA, although they have an immunosuppressive effect. There is no evidence that the use of MTX increases the incidence of NTM infection. Hence, the careful continuation of MTX is an alternative choice. Nevertheless, Mori et al. reported a case in which *M. abscessus* lung disease rapidly progressed during treatment with 12 mg/week of MTX and 15 mg/day of prednisolone (PSL) (14). In the current case, we discontinued the dose of MTX because the patient’s productive cough and hemoptysis continued despite the withdrawal of TCZ. IGU is a newly developed DMARD that was approved in Japan in September 2012. A double-blind, placebo-controlled study of IGU in Japanese patients with RA showed a 20% improvement rate based on the American College of Rheumatology criteria, being almost equivalent to the effect of SASP (24). In a phase III clinical trial, the incidence of infectious disease was 1.5% (2/131) in the IGU group, 2.0% (3/147) in the SASP group and 4.4% (3/68) in the placebo group, and no statistically significant differences were noted in the incidence of adverse reactions between the subjects treated with IGU and SASP (24, 25). In the present case, we changed TCZ and MTX to IGU and SASP, immunomodulators and not immunosuppressants, which resulted in the successful control of the RA activity.

Various reports have documented the reintroduction of biological DMARDs after treatment for MAC pulmonary infection or successful MAC treatment with the continuous use of biological DMARDs (26, 27). In addition, the Japan College of Rheumatology guidelines for the use of biological DMARDs were recently modified (28). However, the continuation or resumption of biological DMARDs is contraindicated in patients who develop pulmonary NTM disease caused by RGM, including *M. abscessus*. Although *M. abscessus* pulmonary infection is rare in Japan, clinicians must keep the potential for this disease in mind when treating patients with RA.

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

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References


