An Autopsy Case of *Mycobacterium abscessus* Pulmonary Infection Complicated with Rheumatoid Arthritis

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Abstract

We present the case of a 70-year-old man diagnosed with *Mycobacterium abscessus* pulmonary infection complicated with rheumatoid arthritis who was treated with corticosteroids. He died despite treatment according to the recommended regimen of imipenem, clarithromycin, and amikacin. Autopsy revealed granulomatous lesions throughout the bilateral lungs. We conclude that *M. abscessus* infection may have a fatal outcome because of the drug resistance of the pathogen. This case suggests that rheumatoid arthritis might be a risk factor for *M. abscessus* pulmonary infection, but further studies are necessary for clarification.

Key words: *Mycobacterium abscessus*, drug resistance, rheumatoid arthritis, corticosteroid

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Introduction

Mycobacterium abscessus is a species of rapidly growing mycobacteria (RGM), and from among RGM, it is the most common pathogen causing pulmonary infection (80%). Further, it is resistant to conventional antibiotics and anti-tuberculosis agents. Although it is susceptible to imipenem (IPM), clarithromycin (CAM) and amikacin (AMK), no effective drug regimen has been firmly established. The prognosis is poor, and there are few reports of successfully treated cases or autopsy cases of the lethal disease (1, 2).

Case Report

In April 2002, a 70-year-old man was admitted to our hospital because of complaints of fever and productive cough. He had a past history of admission due to bronchopneumonia in August 2001. During the past admission, *M. abscessus* was detected in a sputum culture on one occasion, but the organism was not considered pathogenic. His symptoms and findings from chest scans improved shortly after treatment with conventional antibiotics; hence, he was discharged without further study. Although he occasionally experienced relapsing pyrexia after discharge, we assessed his

condition as aspiration pneumonia. He was admitted this time because his symptoms did not improve despite conventional treatment.

The patient had been diagnosed with rheumatoid arthritis (RA) with lung fibrosis (Fig. 1), and oral prednisolone had been administered for 10 years. His medical history included old tuberculosis, emphysema, and peptic ulcer disease from 20 years earlier. He had smoked 30 cigarettes a day for 40 years. He had no family history of any significant disease.

On admission, he was malnourished and appeared chronically ill. His consciousness was drowsy. His height was 160 cm, and body weight was 33.4 kg. Body temperature was 38.5°C, and blood pressure was 80/50 mmHg. His heart rate was 100 beats per minute, and respiratory rate was 20 breaths per minute. Coarse crackles and rhonchi were heard over the bilateral lungs. Deformity of the joints was documented, but no lymphadenopathy was observed. Blood examination revealed a white cell count of 18,900/ μ L and C-reactive protein concentration of 8.3 mg/dL. Blood chemistry showed no remarkable findings, except a rheumatoid factor of 70.5 IU/mL and a slight elevation in aspartate aminotransferase levels. Arterial blood gas values while breathing ambient air were pH, 7.454; pCO₂, 33.7 mmHg; pO₂, 79.1 mmHg; base excess, 0.9 mmol/L; HCO₃⁻, 23.6 mmol/L; and arterial oxygen saturation (SaO₂), 96.3%. A

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Figure 1. Chest radiographs.

Figure 2. Computed tomography scans of the chest.

Figure 3. Cavitory lesion in the right upper lung (Microphotograph, Hematoxylin and Eosin staining, $\times 1$).

chest radiograph obtained in August 2001 (Fig. 1) revealed a cavitory lesion with surrounding dense consolidation that was not observed in the scan obtained in October 2000. A computed tomography scan of the chest confirmed a huge cavity with a dense wall in the patient's right upper lobe (Fig. 2).

Smears and cultures of the sputum for acid-fast bacilli

Figure 4. Granuloma in the cavity wall (Microphotograph, Hematoxylin and Eosin staining, $\times 40$).

yielded positive results on 3 successive occasions. The isolate was identified as *M. abscessus* by DNA-DNA hybridization (DDH Mycobacteria; Kyokuto, Tokyo, Japan) (3). A drug susceptibility test by broth microdilution method (4) revealed the following susceptibilities of the isolated *M. abscessus* to various drugs: AMK, $<16 \mu\text{g/mL}$; IPM, $<4 \mu\text{g/mL}$; levofloxacin, $>4 \mu\text{g/mL}$; ciprofloxacin, $>2 \mu\text{g/mL}$; and minocycline, $>8 \mu\text{g/mL}$. A regimen of IPM/CS (30 mg/kg, i. v.), AMK (6 mg/kg, i.v.) and CAM (12 mg/kg, per os) was started. Despite this treatment, the patient's symptoms and findings from chest scans did not show any improvement. Progressive respiratory failure ensued, and the patient died 4 months later.

On autopsy, both upper lungs were occupied by irregular cavities. Multiple granulomas with caseous necrosis were observed all over the bilateral lungs, particularly around the cavities (Figs. 3, 4). Acid-fast bacilli were recognized within the granulomas by Ziehl-Neelsen staining (Fig. 5). Granulomas were also found in the visceral pleura and hilar lymph nodes (Fig. 6). Diffuse fibrosis with cystic changes and pleural thickening were observed mainly in the lower lungs. There were no remarkable findings in other organs.

Figure 5. Acid-fast bacilli in the granuloma (Microphotograph, Ziehl-Neelsen, ×400).

Figure 6. Granuloma in the hilar lymph node (Microphotograph, Hematoxylin and Eosin staining, ×40).

Discussion

M. abscessus is a species of rapidly growing mycobacteria (RGM) that belongs to the group of non-tuberculous mycobacterium (NTM) (1, 2). It can cause severe pulmonary infection, and there are few successfully treated case reports in the literature because of the multi-drug resistance of the bacteria (5-9). Griffith et al discussed the details of RGM pulmonary infection and reported that the prognosis of *M. abscessus* pulmonary infection is poor and that the mortality rate is 20% (2). Relapse after remission is frequent, and successful treatment of *M. abscessus* pulmonary disease is considered difficult. In the present case, *M. abscessus* was first detected in the sputum in August 2001, but the diagnostic criteria established by the American Thoracic Society in 1997 were not satisfied because the criteria required 2 or more cultures that were positive for the pathogen (10). Before the patient was diagnosed with *M. abscessus* infection, he had experienced relapsing pyrexia. His condition improved with conventional antibiotic therapy, and specific treatment was not started. That delay in diagnosis may have caused the disease to worsen. Although we treated him with the recommended regimen of CAM, IPM/CS and AMK for more than 4 months after diagnosis, the patient died. It is not clear why these drugs were not effective despite the susceptibility of the pathogen to these drugs in an *in vitro* drug susceptibility test.

Autopsy revealed multiple necrotizing granulomatous lesions with acid-fast bacilli over almost the entire area of both lungs. This finding implies that the disease remained severe, regardless of the long-term treatment. The huge cavitary lesion on the right upper lobe was not observed on chest radiographs until 1 year previously. The wall of the cavity comprised necrotizing granulomatous lesions. Active granulomatous changes caused destruction of the structure

of the patient's upper lungs and cavity formation for approximately 1 year. Fibrous changes, probably due to RA, were observed around the bilateral lower lungs. It is unclear if these changes predisposed our patient to NTM infection.

The present patient had a history of RA treated with corticosteroids, gastric ulcer, and underlying pulmonary lesions. These are all regarded as predisposing factors of NTM pulmonary diseases. Griffith et al regarded gastro-oesophageal disorders with chronic aspiration and old tuberculosis, but not treatment with RA, corticosteroid, or immunosuppressive agents, as risk factors of RGM pulmonary infection (2). Dreisin et al identified a relationship between RGM pulmonary disease and RA (9); however, other reports support that RA is a risk factor of NTM infection. RA patients tend to be immunosuppressed because of the underlying disease and its treatment. Further, pulmonary lesions due to RA would complicate the pathology of NTM pulmonary diseases. Origuchi et al reported 2 cases of *Mycobacterium avium* pulmonary infection associated with RA (11). They suggested that RA would be associated with NTM pulmonary diseases even in the absence of treatment with immunosuppressant agents. Watkin et al reported a case of *Mycobacterium kansasii* pulmonary disease with RA and discussed whether the suppression of cellular immunity or immunosuppression mediated by neutrophils would increase the tendency of infection in RA patients (12). In recent times, more aggressive treatment of RA with biological drugs is recommended. The risk of NTM pulmonary infection among RA patients would increase under such a condition that had not been previously experienced (13), and we should be cautious of opportunistic infections, including NTM.

In the present case, granulomatous lesions were found not only in the lungs but also in the hilar lymph nodes and visceral pleura. The lesions of tuberculosis are said to spread through 3 courses: 1) endobronchial spread, 2) contiguous spread, and 3) lymphohematogenous spread (14). In cases of

primary tuberculosis, lesions of the mediastinal or hilar lymph nodes are frequently observed. In secondary tuberculosis (affecting adults), the lesions tend to localize within the lungs. There are no case reports of NTM pulmonary diseases with lesions infiltrating into the mediastinal or hilar lymph nodes, except cases of acquired immunodeficiency syndrome (AIDS) patients. The present case might suggest the possibility of extrapulmonary spread of NTM infection in patients other than AIDS patients.

We present an autopsy case of *M. abscessus* pulmonary infection associated with RA. The patient died despite treatment with the standard regimen to which the pathogen was susceptible in an *in vitro* drug susceptibility test. RA is suggested as a risk factor of NTM pulmonary infection.

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