Pulmonary Infection of *Mycobacterium avium-intracellulare* Complex with Simultaneous Organizing Pneumonia

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**Abstract**

A 67-year-old woman presented high-grade fever and dyspnea. Sputum culture confirmed *Mycobacterium avium-intracellulare* complex (MAC). Transbronchial lung biopsies revealed organizing pneumonia (OP) that was rapidly improved with corticosteroid. Five months after onset, a nodule emerged in the right lung. Although MAC was confirmed, the lesion was deemed too small to merit anti-mycobacterial chemotherapy. Four months later, diffuse infiltrates developed on chest X-ray. Bronchoalveolar lavage study identified MAC and exhibited OP patterns. We commenced anti-mycobacterial chemotherapy. The infiltrates almost completely improved within a month without corticosteroid.

**Key words:** *Mycobacterium avium-intracellulare* complex, organizing pneumonia, immune reaction, corticosteroids

(DOI: 10.2169/internalmedicine.45.1217)

**Case Presentation**

First admission

A 67-year-old woman visited a hospital on April 24, 2001 because of a high-grade fever and cough that had begun the night before. Her condition was initially diagnosed as pneumonia due to infiltrates in the right upper lung field of her chest X-ray (CXR). However, a sputum smear tested positive for mycobacterium and the patient was transferred to the Kyoto University Hospital on suspicion of pulmonary tuberculosis on April 27. The patient had no family history that could have contributed to the condition. She had undergone two operations while still in her fifties: a left-sided thyroidectomy due to adenoma at the age of 55 (precise information not available) and a cholecystectomy due to a gallstone at the age of 57. She did not smoke cigarettes or drink alcohol, and she had not recently fed any pets.

Her physical status was almost normal except for a body temperature of 37.6°C and audible fine crackles in the right upper lung field. Blood samples showed a white blood cell count of 5.4×10⁹/l with a normal pattern of cell differential,
Figure 1. Chest images taken on the 11th hospital day. (A) Chest X-ray showed infiltrates with air bronchogram in the right upper lung field and the medial lower lung field. (B) Chest HRCT showed widely spread patchy air-space consolidations and ground glass attenuations surrounded by intralobular reticular patterns in the right upper lobe. These findings suggested organizing pneumonia. (C) Chest CT (mediastinal window) of the right upper lobe where the primary infectious site was considered to exist. Within air-space consolidations any nodular lesion is undetectable (compare with Fig. 3B). (D) Chest X-ray taken before discharge showed marked improvement.

Since mycobacteria were also detected from her sputum smear obtained on admission, she was immediately started on a regimen of anti-tuberculous chemotherapy with rifampicin (450 mg/day), pyrazinamide (1200 mg/day), isoniazid (300 mg/day), and levofloxacin (300 mg/day). The therapy provided little benefit, however, and her high-grade fever and respiratory symptoms showed no improvement. On the 11th hospital day infiltrates spread into the lower lung fields on CXR (Fig. 1A). HRCT performed on the same day revealed a series of patchy, widely dispersed air-space consolidations and accompanying ground-glass attenuations (GGA) in the right upper lobe (Fig. 1B, C). *M. intracellulare* was identified from the sputum culture on the 14th hospital day. Pyrazinamide and isoniazid were replaced by clarithromycin (400 mg/day).

Over the next two weeks her symptoms and hypoxemia gradually deteriorated. Bronchoalveolar lavage (BAL) and transbronchial lung biopsy (TBLB) were performed on the 24th hospital day. The BAL fluid findings suggested extrinsic allergic reactions rather than infectious disorders (Table 1). TBLB specimens obtained from the lateral segment of the right upper lobe showed organizing pneumonia (OP) patterns (Fig. 2).

Based on these results and her clinical course, we concluded that the primary condition was OP due to unknown...
etiology and that the secondary condition was latent infection with *M. intracellulare*. Anti-mycobacterial therapy was temporarily discontinued and prednisolone (PSL) therapy (50 mg/day) was introduced on the 28th hospital day. Her physical status and infiltrates on CXR improved remarkably within a few weeks (Fig. 1D). PSL was tapered. She was discharged on the 64th hospital day, when the PSL daily dose was 20 mg.

**Second admission**

Five months after onset, during ongoing PSL treatment tapered down to 10 mg/day, a nodular shadow emerged at the apical portion of the right lung. Cultures of brushing and bronchial washing samples obtained with bronchoscopy were positive for mycobacterium, and a DNA study identified *M. intracellulare*. In view of the small size of the lesion and absence of symptoms, however, we decided to observe the patient without administering anti-mycobacterial chemotherapy. Four months later, during ongoing PSL treatment tapered down to 5 mg/day, diffuse infiltrates emerged on CXR and the patient was readmitted (Fig. 3A).

The patient was afebrile and blood tests revealed no abnormal values other than mildly elevated ESR (30 mm/hr) and CRP (1.0 mg/dl). Chest HRCT revealed bilateral airspace consolidations, varied GGAs, and the nodule in the right posteroapical portion that had been already diagnosed as *M. intracellulare* infection (Fig. 3B-E). Arterial blood gas values were normal. MAC was identified in BAL fluid obtained from the right middle and lower lobes, and the cell differential pattern of BAL fluid obtained from the right middle lobe indicated OP patterns (Table 1). In view of her mild respiratory symptoms, we chose anti-MAC chemotherapy (rifampicin 450 mg+ethambutol 750 mg+clarythromycin 400 mg a day) without changing the PSL dose. One month later the disease significantly improved and the patient was discharged (Fig. 3F). PSL was discontinued soon after discharge. Antimycobacterial chemotherapy was continued for 18 months up to August of 2003. No relapse has been observed as of this writing in May 2005.

**Discussion**

The initial diagnosis of OP was based upon findings from chest radiographs, BAL studies, pathologic studies, and the patient’s response to corticosteroid treatment. The identifica-
Figure 3. Chest images taken on the second admission. (A) Chest X-ray showed a nodular shadow in the right upper field and bilateral infiltrates. (B-E) Chest HRCT revealed various patterns; a nodule in the right posteroapical portion (B, mediastinal window), air-space consolidations (C, right middle lobe; D, right lower lobe), and ground glass attenuations (E, left upper lobe). Figure 3C, 3D, and 3E showed patterns compatible with organizing pneumonia. (F) Chest X-ray taken before discharge showed improvement of infiltrative shadows in the right middle lung field.

The identification of *M. intracellulare* on the first admission confirmed the presence of the MAC infection. In spite of the identification of the MAC infection in the background, the patient exhibited no active granulomatous lesion of sufficient scale to show up on the CT scan or tree-in-bud appearance. At the same time, the clinical manifestation was prominent OP that...
induced severe respiratory distress. Pulmonary lesions, as well as respiratory symptoms, promptly improved in response to corticosteroids alone.

On the second admission, although pathologic examination was not available, BALF studies confirmed MAC infection and suggested an immunologic reaction (Table 1). In addition, the similarity of clinical findings and data of two admissions was suggested, especially in chest CT images and cell differential of BALF (Tables 1, 2).

According to the cultures of sputum and BAL fluid, MAC infection was definite throughout the disease. However, the patient simultaneously presented OP at the first admission. At the second admission, although histopathologic confirmation was lacking, HRCT findings and cell differential of BAL fluid suggested the presence of OP. We, therefore, speculated that the serial pulmonary disease in the present case might be an infectious variant of MAC. It seemed to have two aspects; one was an infectious disease of MAC; the other was OP. Since OP was severe on the first admission, corticosteroid therapy was essential. On the second admission, however, the reduced severity of respiratory symptoms did not call for the repeated use of corticosteroids and anti-mycobacterial therapy was sufficient to improve all of the pulmonary lesions.

Two factors were thought to contribute to the recurrence. First, our failure to treat the primary site of the MAC infection probably provided the bacilli the opportunity to grow and spread to other regions. Secondly, the tapered dose of PSL (5 mg/day at the recurrence) might have been insufficient to suppress the OP. However, we also speculated that the corticosteroid therapy could suppress the OP to some extent and reduced the severity in spite of the tapered doses. Successful treatment of the recurrent disease with anti-MAC chemotherapy alone suggested that MAC infection was the principal cause of her serial pulmonary disease.

Marchevsky et al reported MAC in as many as 24 (60%) of 40 cases whose cultures of surgically resected lungs were positive for mycobacteria (4). They also described the relation between chest images and histological findings in their population. Interstitial fibrosis or OP corresponded to bilateral interstitial shadows in 7 cases (17.5%) confirmed to be infected with either the MAC or M. gordonae. Further, all 3 cases (7.5%) with multiple infiltrates on CXR were positive for MAC. Pulmonary infection with MAC can present varied clinical manifestations and pathohistological features. By no means can it be considered a mere infectious disease. If the immunologic background of the hosts vary, its clinical manifestations should vary accordingly (4, 9).

MAC has been reported to induce the production of certain cytokines, including interleukin-1, interleukin-6, tumor necrosis factor-alpha, granulocyte-monocyte colony-stimulating factor, and granulocyte colony-stimulating factor (10-13). Rao et al proposed that a monocyte chemoattractant protein-1-like molecule on M. avium might generate a local immune response (14). Recently, aerosolized MAC has been reported to cause hypersensitive reactions called “hot tub lung”. It resembled hypersensitivity pneumonitis clinically, radiologically, and pathologically and was well treated with corticosteroids (5-8). It would not be improbable that MAC had the potential to trigger OP.

The CD4+/CD8+ ratio of BALF lymphocytes is usually lower than 1 in patients with cryptogenic OP (COP) or collagen vascular disease-associated OP (CVD-OP) (15). In the present case, the ratio was higher than 1 (Table 1). The same finding has been reported in cases with drug-induced and radiation-induced variants of OP (16, 17). Nonetheless, further investigations need to be conducted to determine whether the CD4+/CD8+ ratio of BALF lymphocytes can be reliably used to discriminate OP with extrinsic causes from COP and CVD-OP. The significantly increased plasma cells in the first BALF in the present case also suggested that the OP had been induced by an allergic reaction to an extrinsic antigen (18).

In conclusion, pulmonary MAC infection can present various clinicopathologic features according to the various immune responses of the hosts. Further studies are needed to confirm whether or not OP is one of those features.

We thank Dr. Masanori Kitaichi at the Laboratory of Anatomic Pathology and Dr. Katsuhiro Suzuki at the Department of Infectious Diseases, Clinical Research Center, HHO Kinki-chuo Chest
Medical Center, Osaka, Japan. Dr. Kitaichi offered precise comments on the pathologic findings in the present case, and Dr. Suzuki advised us on the treatment for pulmonary mycobacteriosis in the present case. We also thank Mr. Simon Johnson for checking the linguistic problems. This report was originally presented at the 59th Kinki Divisional Meeting of the Japan Respiratory Society on June 29, 2002.

References

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