Mixed Pulmonary Infection with Three Types of Nontuberculous Mycobacteria

Yu Kurahara¹, Kazunobu Tachibana¹², Kazunari Tsuyuguchi² and Katsuhiro Suzuki¹

Abstract

A 71-year-old man with a history of chronic obstructive pulmonary disease (COPD) and silicosis was referred to our hospital for evaluation of dyspnea. A progressively enlarging cavity found in the patient’s left lower lung was associated with a worsening respiratory status. One year after the initial referral, the patient was diagnosed with nontuberculous mycobacterial (NTM) infection. We herein report the case of a patient with a mixed infection of M. kansasii, M. avium complex and M. abscessus, the various organisms having been isolated in succession. Recognizing a diagnosis of mixed pulmonary NTM infection is therefore crucial in patients with underlying diseases.

Key words: nontuberculous mycobacterium, mixed infection

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Introduction

Nontuberculous mycobacteria (NTM) have been isolated worldwide and are increasingly recognized to be pathogens in humans, with pulmonary disease being the most frequent manifestation (1, 2). The most common pathogens are Mycobacterium avium complex (MAC), M. kansasii and rapidly growing mycobacteria (RGM) (1). Patients infected with MAC are sometimes coinfected with other types of NTM, especially those who are immunosuppressed. We herein report the case of a patient with a mixed pulmonary infection of MAC, M. kansasii and M. abscessus, the various organisms having been isolated in succession.

Case Report

A 71-year-old man with a 12-year history of silicosis and chronic obstructive pulmonary disease (COPD) was referred to our hospital for evaluation of dyspnea on exertion. He had worked as a silicon carbide smelter for forty years and had a smoking history of more than 800 pack-years. On admission, chest X-ray and computed tomography showed bilateral bullae and multiple calcified consolidations throughout both lung fields, consistent with diagnoses of COPD and silicosis (Figs. 1, 2a). No daughter nodules or bronchiectasis were observed. Pulmonary function tests revealed expiratory flow limitation: the forced expiratory volume in one second (FEV1) was 0.56 L/s (26% of the predicted value) and the forced vital capacity (FVC) was 1.71 L (70% of the predicted value). The patient’s sputum smear was negative for acid-fast bacilli. He had been visiting our hospital monthly for treatment with tiotropium bromide hydrate and pulmonary rehabilitation.

One year after his first referral, the patient presented with arterial oxygen desaturation. On examination, he was found to have a heart rate of 80 beats/min, a blood pressure of 142/76 mmHg, a respiratory rate of 16 breaths/min, a temperature of 36.8°C and an oxygen saturation of 92% at rest on room air. He was severely emaciated, with a body mass index of only 16.5 kg/m². An arterial blood analysis performed with oxygen supplied by nasal cannula at 0.5 L/min showed mild hypoxia with a pH of 7.34, a PaCO₂ level of 42 mmHg, a PaO₂ level of 63 mmHg and an HCO₃⁻ level of 31 mEq. A laboratory evaluation revealed a white blood cell count of 6,800/cm³ (70.8% segmented neutrophils), a C-reactive protein level of 0.78 mg/dL and an erythrocyte sedimentation rate of 44 mm/h. An ELISA test for HIV-1/2 was

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negative. Chest radiography showed a new cavity lesion in the lower lobe of the patient’s left lung (Fig. 2b). We suspected a diagnosis of active pulmonary tuberculosis, given that the cavity had significantly increased in size over the year since the patient’s initial presentation. A sputum smear was positive for acid-fast bacilli; however, the cultured isolates were identified as M. kansasii three times. We initiated treatment with home oxygen therapy and chemotherapy for M. kansasii using isoniazid (200 mg/day), rifampicin (300 mg/day) and ethambutol (500 mg/day). In spite of this therapy, the patient experienced increasing difficulty in breathing as he gradually lost strength.

Six months later, he was brought to our hospital by ambulance presenting with hemoptysis. This time, both MAC and M. kansasii were isolated. Chemotherapy with a combination of isoniazid, rifampicin and ethambutol had little effect on the patient’s pulmonary disease, and we substituted clarithromycin (600 mg/day) for isoniazid in order to target both MAC and M. kansasii. However, the lower left lobe cavitation and giant bullous emphysema in the right middle lobe continued to increase in size (Fig. 2c). M. abscessus was isolated seven months after the start of the second treatment regimen (for full sputum culture results see Table). We commenced intravenous therapy with imipenem/cilastatin (1.5 g/day) and amikacin (300 mg/day); however, the treatment was unsuccessful in slowing the progression of the patient’s infection. Additional blood tests were negative for Aspergillus galactomannan antigen, (1-3)-β-D-glucan and tumor markers (cinoembryonic antigen, cytokeratin 19 fragment and progastrin-releasing peptide). The cavitary lesion continued to increase in size (Fig. 2d) until the patient’s death from severe respiratory failure, fifteen months after the first isolation of M. kansasii.

All positive results for M. kansasii, MAC and M. abscessus were confirmed using DNA-DNA hybridization tests (DDH Mycobacteria®; Kyokuto, Tokyo, Japan) of at least three separate expectorated sputum samples. The M. kansasii isolate was found to be susceptible to rifampicin (40 μg/mL), as determined using the proportion method with Ogawa egg-based medium (Wellpack®; Japan BCG Laboratory, Tokyo, Japan). The MAC isolate was found to be susceptible to clarithromycin with a MIC of 4 μg/mL, as determined using the broth microdilution method (BrothMIC NTM®; Kyokuto, Tokyo, Japan). The M. abscessus isolate was found to be susceptible to amikacin with a MIC of 8 μg/mL and intermediate susceptible to imipenem/cilastatin with a MIC of 16 μg/mL, as determined with the broth microdilution method.

Discussion

NTM are ubiquitous acid-fast organisms that are found worldwide (1). Before the emergence of the human immunodeficiency virus (HIV), mycobacterial infections were primarily caused by M. tuberculosis. However, mixed NTM infections associated with immune suppression have been reported in HIV patients (3, 4), and it is likely that their true prevalence is unknown or underestimated due to the lack of morphologic differentiation between colonies in mixed cultures. A retrospective review revealed that 29% of MAC patients have mixed infections with other NTM, including M. chelonae, M. simiae, M. fortuitum and M. abscessus (5). Similarly, 55% of M. abscessus patients have coexistent MAC infection or a history of the same (6). However, to our knowledge, this is the first report of a single patient with a mixed infection of three or more types of NTM.

Pulmonary NTM disease commonly presents in one of two forms: fibrocavitary or nodular/bronchiectatic (1). While MAC and M. abscessus are associated with both forms of the disease, M. kansasii is predominantly associated with the former. In the present case, the patient died after experiencing a rapidly progressive clinical course and a continuously enlarging cavitary lesion. All three strains of NTM isolated from the patient have the potential to cause pulmonary cavitary lesions. Generally, fibrocavitary MAC is particularly destructive and rapidly progressive with a high mortality rate (7). However, the patient had concomitant COPD and an emphysematous bulla also became enlarged. Therefore, concomitant COPD and NTM may be linked to the poor outcome observed in the present case.

In the present case, the MAC isolate was found to be susceptible to clarithromycin, and the M. kansasii isolate was found to be susceptible to rifampicin, suggesting that both of these strains should have responded to appropriate chemotherapy. However, M. abscessus is one of the most difficult RGM to treat because it is resistant to standard anti-tuberculosis agents (6). Furthermore, although it is susceptible to imipenem/cilastatin, clarithromycin and amikacin, no effective drug regimens for M. abscessus have yet been established. In their evaluation of RGM pulmonary infections, Jarand et al. reported poor prognoses for patients with M. abscessus pulmonary infection, with a mortality rate of 16% (6). While it is highly likely that M. abscessus infection was a primary cause of death in the present case, the...
with three different types of NTM in short succession. Increased the patient’s susceptibility to mixed infections resulting in chronic immune suppression. Both of these factors also a primary cause of the patient’s malnutrition, which resulted in such a severe clinical course. These diseases were seen during the later stages of the patient’s disease progression after treatment for M. kansasii and MAC infection (Table). Generally, cystic fibrosis, prior granulomatous disease and lipoid pneumonia are risk factors for pulmonary RGM infection (9, 10). Therefore, potential lung damage was likely a risk factor for M. abscessus development in the present case. Although there is no consensus as to the likelihood of NTM microbial substitution, the current guidelines (1) for the treatment of MAC and M. kansasii may need to reference microbial substitution if the risk can be verified.

We herein reported a rare case of mixed pulmonary infection with three species of NTM. Because the various strains may mimic each other, it is likely that many cases of mixed NTM infection are missed or misdiagnosed as single-organism NTM infections, resulting in the prescription of inappropriate antibiotics. Physicians should therefore pay careful attention when diagnosing NTM infection, especially in patients with severe underlying lung disease.

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

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We thank S. Yoshida (Kinki-Chuo Chest Medical Center, Clinical Research Center) for measuring the MIC of M. abscessus.

**References**


Table. Sputum Cultures of NTM

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three different NTM may thus have acted additively in the patient’s clinical course.

Most patients with NTM have underlying lung diseases such as COPD, bronchiectasis, pneumoconiosis or healed tuberculosis (1). In the present case, the patient’s multiple underlying lung diseases (which included COPD, silicosis and chronic respiratory failure) may account for why he experienced such a severe clinical course. These diseases were also a primary cause of the patient’s malnutrition, which resulted in chronic immune suppression. Both of these factors increased the patient’s susceptibility to mixed infections with three different types of NTM in short succession.

A case series investigating pulmonary M. abscessus infection suggested that M. abscessus infection might progress as a result of microbial substitution during the course of MAC treatment (8). This is consistent with the findings observed in the present case, in which M. abscessus was isolated during the later stages of the patient’s disease progression after treatment for M. kansasii and MAC infection (Table). Generally, cystic fibrosis, prior granulomatous disease and lipoid pneumonia are risk factors for pulmonary RGM infection (9, 10). Therefore, potential lung damage was likely a risk factor for M. abscessus development in the present case. Although there is no consensus as to the likelihood of NTM microbial substitution, the current guidelines (1) for the treatment of MAC and M. kansasii may need to reference microbial substitution if the risk can be verified.

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