

Nontuberculous Mycobacterial Lung Disease Caused by *Mycobacterium terrae* in a Patient with Bronchiectasis

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We report a rare case of lung disease caused by *Mycobacterium terrae* in a previously healthy woman. A 45-year-old woman was referred to our hospital due to a chronic cough with sputum. A computed tomography scan of the chest revealed bronchiolitis in conjunction with bronchiectasis in both lungs. Nontuberculous mycobacteria were identified and isolated from the bronchoalveolar lavage fluid collected from each lung. All isolates were identified as *M. terrae* by various molecular methods that characterized the *mpoB* and *hsp65* gene sequences. Antibiotic therapy using clarithromycin, rifampin, and ethambutol improved the patient's condition and successfully resulted in sputum conversion.

Key Words: Bronchiectasis; Mycobacterium Infections, Nontuberculous

Introduction

Mycobacterium terrae complex is known to comprise multiple species, including *M. terrae*, *M. non-chromogenicum*, and *M. trivialis*¹. *M. terrae* is ubiquitous in the environment and generally considered a non-pathogenic nontuberculous mycobacteria (NTM)¹. The most common presentation of *M. terrae* infection is tenosynovitis of the upper extremities, often following trauma^{2,3}. To date, few cases of NTM lung disease caused by *M. terrae* have been reported. Here, we report a very rare case of *M. terrae* lung disease associated with bronchiectasis in an immunocompetent patient.

Case Report

In March 2008, a 45-year-old woman was referred to our hospital due to chronic cough and sputum. The patient had been healthy until two months earlier, when cough and purulent sputum developed. She had a history of smoking (10 pack-years), but had stopped 10 years prior. The patient had pectus excavatum. Laboratory results were normal with the exception of elevated CA 19-9 (75.32 U/mL, normal range, 0~37 U/mL). Her height was 161 cm and body weight was 51 kg. A human immunodeficiency virus (HIV) antibody test was negative.

A computed tomography (CT) scan of the chest revealed bronchiectasis and bronchiolitis in both lungs (Figure 1A). The patient also had pectus excavatum in the anterior chest wall. There was no evidence of cystic fibrosis or other common causes of bronchiectasis. NTM were isolated from bronchoalveolar lavage fluid collected from both lungs and cultured *in vitro*.

Polymerase chain reaction (PCR) restriction fragment length polymorphism analysis (PRA) was used to identify the particular mycobacterial species isolated from the

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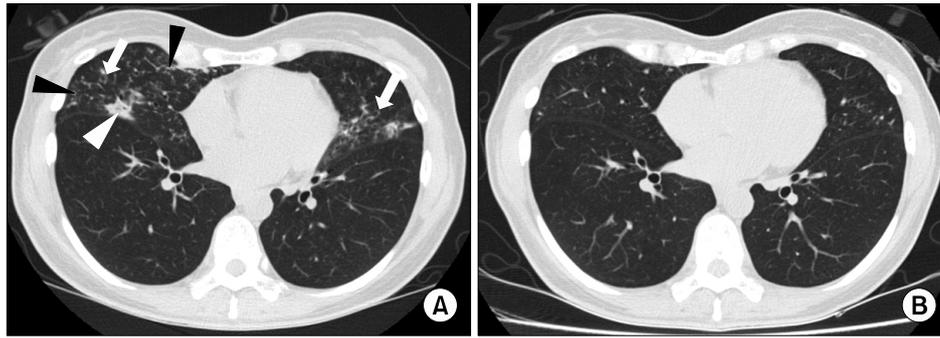


Figure 1. A 45-year-old woman with bronchiectasis and nontuberculous mycobacterial lung disease caused by *Mycobacterium terrae*. (A) A transverse CT scan (2.5-mm-section thickness) obtained on level with the right inferior pulmonary vein at the time of presentation, before treatment, reveals bilateral bronchiectasis (arrows) in the right middle lobe and the lingular segment of the left upper lobe, as well as cellular bronchiolitis with tree-in-bud signs (black arrow heads) in both lungs. Lobular consolidation in the right middle lobe (white arrow heads) was also noted. (B) A CT scan of the same patient after 12 months of antibiotic therapy revealed a decrease in the extent of cellular bronchiolitis and lobular consolidation in both lungs. CT: computed tomography.

patient. DNA was extracted from pure culture colonies of mycobacteria grown on 7H10-OADC agar plate and the genes *rpoB* and *hsp65* were amplified by PCR. PCR product was digested using the restriction enzymes *MspI* and *HindIII* as described previously^{4,5}. The pattern of the resulting DNA fragments was then compared to those kept in a database of known mycobacterial species. PRA of the *rpoB* gene resulted in fragment lengths of 110, 95, 55, and 45 bp using *MspI* and 175, 55, and 45 bp using *HaeIII* (Figure 2). These DNA fragment lengths matched the known restriction fragment patterns of the reference strain of *M. terrae* ATCC15755 reported in the previous studies^{5,6}. The identity of etiological agent was also confirmed by sequencing analysis, revealing 99 and 100% sequence similarity with the *rpoB* gene (GenBank accession no. AF057488.1) and *hsp65* gene (GenBank accession no. AF547879) of *M. terrae* ATCC15755, respectively.

Drug susceptibility testing was performed using a broth microdilution method, as previously described for slow growing mycobacteria, such as *M. kansasii*, according to the guidelines of the Clinical and Laboratory Standards Institute (CLSI)⁷. The clinical isolate of *M. terrae* was susceptible to clarithromycin, ethambutol, and amikacin but resistant to ciprofloxacin and rifampin (Table 1).

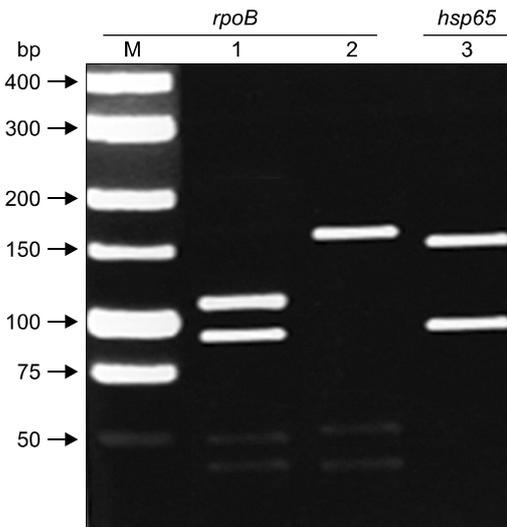


Figure 2. Electrophoresis of the PCR restriction enzyme PRA of the *rpoB* and *hsp65* genes from the clinical isolate of the patient. M, size marker; Lane 1, *rpoB* gene PCR product after digestion by *MspI* Lane 2, PCR product of the *rpoB* gene after digestion by *HaeIII* Lane 3, PCR product of the *hsp65* gene after digestion by *HaeIII*. PCR: polymerase chain reaction; PRA: polymorphism analysis.

The patient was treated with oral clarithromycin (1,000 mg/day), rifampin (600 mg/day), and ethambutol (800 mg/day) for 18 months. The treatment outcome was favorable; the patient's symptoms resolved completely, radiographic findings improved (Figure 1B), and negative

Table 1. Antimicrobial susceptibility patterns for the *Mycobacterium terrae* strain isolated from our patient

| Antimicrobial agent | MIC ($\mu\text{g/mL}$) | Interpretation |
|---------------------|--------------------------|----------------|
| Clarithromycin | $\leq 0,5$ | Susceptible |
| Rifampin | 2 | Resistant |
| Ethambutol | 2 | Susceptible |
| Amikacin | 4 | Susceptible |
| Ciprofloxacin | 8 | Resistant |
| Moxifloxacin | 2 | Intermediate |

MIC: minimum inhibitory concentration.

conversion of sputum cultures was achieved and maintained after 12 months of antibiotic therapy (Figure 1B).

Discussion

Despite the prevailing view that *M. terrae* complex isolates are nonpathogenic, these organisms are occasionally identified in clinical specimens⁸. For example, in our institution, *M. terrae* complex made up 3% of 1,548 NTM clinical isolates during the 2-year period from 2002 to 2003⁹. Nonetheless, no patient had clinically significant disease caused by *M. terrae* complex infection during that time.

NTM lung disease caused by *M. terrae* complex is rarely reported in the literature¹⁰⁻¹², and there is no reported case in Korea. Furthermore, previous studies have had difficulty identifying the exact species of clinical isolates, as commercial DNA probes and high performance liquid chromatography (HPLC) are not suitable methods to distinguish between different member species of the *M. terrae* complex. A recent study analyzing 16S rRNA and *hsp65* genes demonstrated genomic heterogeneity among *M. terrae* complex members¹³. Therefore, we were able to confirm that our patient had *M. terrae* infection using modern molecular techniques that enabled sequencing of the *ipoB* and *hsp65* genes.

NTM lung disease has two distinct radiographic manifestations: an upper lobe fibrocavitary form and a nodular bronchiectatic form¹. The nodular bronchiectatic form of the disease occurs predominantly in non-smoking middle-aged or elderly women who have no

underlying lung disease. The radiographic features of the nodular bronchiectatic form include bronchiectasis and multiple nodules, which tend to be most severe in the lingular segment of the left lung and in the right middle lobe. These features are well characterized in *M. avium* complex lung disease, but have also been noted in NTM lung disease caused by other NTM species, such as *M. abscessus* complex¹⁴⁻¹⁶. In addition, women with the nodular bronchiectatic form of NTM lung disease also often have certain medical conditions, including pectus excavatum, scoliosis, and thin body habitus¹⁷. Our case study presented with typical clinical and radiographic features of the nodular bronchiectatic form of NTM lung disease.

The optimal antimicrobial therapy regimen for *M. terrae* infection has yet to be established. Some have suggested that drug treatment regimen for *M. terrae* infection should include macrolide, rifampin, and ethambutol². Our patient received these three drugs and had substantial improvement without significant sequelae. Despite the rifampin resistant that the clinical isolates exhibited *in vitro*, it was included in the treatment regimen for our patient. It is unclear whether the combination of rifampin and ethambutol proved an additive, or synergistic, effect².

In conclusion, *M. terrae* should be considered a possible etiologic pathogen of the nodular bronchiectatic form of NTM lung disease, despite the rare occurrence of *M. terrae* lung disease. Additionally, macrolide-containing antibiotic therapies may be effective in the treatment of *M. terrae* lung disease.

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