의학석사 학위논문

Clinical Implications of The Isolation of Rare Nontuberculous Mycobacteria (NTM)

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ABSTRACT

Introduction: The isolation of nontuberculous mycobacteria (NTM) from humans has been increasing. Although the clinical implications of common NTM are well-known, the importance of the rare NTM remains unclear. We investigated the clinical implication of the rare NTM.

Methods: Patients with NTM isolation between July 1, 2010, and June 31, 2012, were screened for inclusion. Rare NTM were defined as NTM classes except the seven commonly identified NTM species at Seoul National University Hospital: *Mycobacterium. avium, M. intracellulare, M. abscessus, M. massilence, M. fortuitum, M. kansasii*, and *M. gordonae*. Clinical, radiographic, and microbiological data of patients with rare NTM were reviewed and analyzed.

Results: During the study period, 2,556 NTM were isolated from 1,373 patients. Of 2,556 NTM, species identifications of 805 NTM were performed. Ninety NTM from 84 patients were identified as rare NTM. Among these, *M. peregrinum* was the most common (17 times, 18.5%). The median age of 84 patients was 64 years (range, 26-84 years), and 50 (59.5%) patients were male. The most common underlying diseases were solid organ malignancies, including lung cancer (12 patients, 14.3 %). Sputum (54.8%) and cough (47.6%) were the most common symptom complaints. On radiologic findings, both upper lobes were

commonly involved lesions (right upper lobe in 46 patients and left upper lobe in 40 patients). Multiple nodules were the most commonly observed radiographic findings (49 patients, 58.3%) followed by bronchiectasis (27 patients, 32.1 %) and cavities (16 patients, 19.0 %). Among five patients in whom rare NTM were isolated twice or more times, one in whom rare NTM as well as *M. abscessus* were isolated had progression of radiographic findings and symptoms. In the other three patients, neither aggravation of symptoms nor progression of radiography lesions on chest radiography developed. The other patient in whom *M. chimaera* were isolated three times, developed new centrilobular nodules. However, the symptoms of this patient did not change.

Conclusions: Most of the rarely identified NTM species were identified only once in patients followed by rare clinical aggravation. Clinicians should observe these patients closely without invasive work ups.

Keywords: clinical implication, nontuberculous mycobacterium

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LIST OF ABBREVIATION

NTM: Nontuberculous *Mycobacteria*

BAL: bronchoalveolar lavage

TB: tuberculosis

CT: Computed Tomography

INTRODUCTION

NTM are defined as mycobacteria other than *Mycobacterium tuberculosis* complex and *M. laprae*. Presently, more than 125 classes of NTM species have been identified (1). Since NTM were recognized as possible pathogens in the 1950s (2, 3), the occurrence of NTM lung diseases has been increasing worldwide (4-6). NTM lung disease usually develops among people with underlying lung illnesses, including bronchiectasis and chronic obstructive pulmonary disease (COPD) or with immunosuppressive states from a post-transplantation status or HIV infection (7, 8). However, NTM lung disease has been increasingly identified among people without a definitely underlying pathology (9-14).

Improvements in microbial diagnostic tools may have led to increased isolation of NTM. In addition, the increase in susceptible hosts such as patients with underlying lung disease or immunocompromised state has been attributed to the increase in NTM lung disease (6, 8, 15-17). In South Korea, NTM were isolated in soil at first in 1966, and the first report of isolation of NTM in humans was in 1970 (18). Since the first report of lung disease from NTM in 1981 in South Korea, the rate of NTM isolation has increased steadily (19). In Seoul National University Hospital, a tertiary referral hospital in South Korea, the number of patients from whom NTM were isolated increased from 214 in 2002 to 302 in 2008, whereas the number of patients with culture-proven tuberculosis (TB) decreased from 436 in

2002 to 276 in 2008, respectively (20).

Human diseases due to NTM are classified into four distinct clinical syndromes according to the organs involved: pulmonary disease (*M. avium complex, M. kansasii, M. abscessus, M. xenopi, M. malmoennse*), lymphadenitis (*M. avium complex, M. scrofulaceum, M. malmoense*), cutaneous disease (*M. marinum, M. fortuitum, M. chelonae, M. abscessus, M. ulcerans*), and disseminated disease (*M. avium complex, M. kansasii, M. chelonae, M. haemophilum*) (21). With advances in technologies for the detection for NTM, newly identified species of NTM have continuously been reported. For example, new species such as *M. longobardum* and *M. iranicum* were newly identified in 2012 (22, 23).

Although the clinical characteristics of diseases caused by commonly isolated NTM are well known, those caused by newly and rarely isolated NTM are not fully understood. In the present study, we investigated the frequency of rarely found NTM and the clinical characteristics of patients with rare NTM.

PATIENTS AND METHODS

1. Study population

Patients in whom NTM were isolated once or more from respiratory specimens including sputum, bronchoscopic washing fluid, and bronchoalveolar lavage (BAL) fluid between July 1, 2010, and June 31, 2012, at Seoul National University Hospital were included in the analysis. During the study period, 2,556 NTM were isolated from 1,373 patients. The protocol of this study was approved by the Institutional review board of Seoul National University Hospital.

2. Method of identification of NTM species

Respiratory specimens were decontaminated with 4% sodium hydroxide (NaOH), homogenized, and concentrated by centrifugation at 3000 g for 20 min. The processed sediment was stained using the Ziehl-Neelsen method (24). Concentrated specimens were cultured in 3% Ogawa medium and observed weekly for 9 weeks after inoculation. Once cultured, *M. tuberculosis* and NTM were differentiated using the Gen-Probe® method (Gen-Probe, San Diego, CA, USA) (25). Following isolation of a suspected mycobacterial species, confirmation of NTM was performed by analyzing the sequences of three genes: *16S rRNA, rpoB,* and *tuf*. Polymerase chain reaction (PCR) and subsequent sequencing were performed, and the resulting sequences were compared to those of the reference database using the basic local

alignment search tool (BLAST). Mycobacterial species were identified using *16S rRNA* sequences and the algorithm described in the Clinical and Laboratory Standards Institute guidelines MM18-A (26).

3. Definition of rare NTM

Rare NTM were defined as NTM species other than *M. avium, M. intracellulare, M. abscessus, M. massilence, M. fortuitum, M. kansasii,* and *M. gordonae* which were the seven commonly identified NTM species at Seoul National University Hospital.

4. Clinical and radiological findings of the patients

Demographic, clinical, and radiographic data of the included patients in whom rare NTM were isolated were reviewed. Demographic data including age, gender, and smoking habits; past medical history of TB, measles, pertussis, and sinusitis; comorbidities including malignancy, diabetes mellitus, cerebrovascular disease, rheumatologic disease, inflammatory bowel disease, and gastroesophageal reflux disease, and underlying lung disease; clinical data of symptoms for which the patient complained; and findings of physical examination were thoroughly reviewed. The characteristics and distribution of lung lesions were analyzed based on chest computed tomography (CT).

RESULTS

1. Common NTM isolated from respiratory specimens during the study period

During the study period, 2,554 NTM were isolated from 1,373 patients. Of these, 803 NTM were identified. Among them, 713 (88.6%) were commonly isolated species. *M. avium* (250 specimens, 35.1%) and *M. intracellulare* (252 specimens, 35.4%) were the most common species followed by *M. abscessus* (93 specimens, 13.0%). All of the classes of common NTM revealed in the study population are described in Table 1.

Table 1. Common NTM isolated from respiratory specimens

NTM ID	N (%)
Mycobacterium avium complex	
Mycobacterium avium	250 (35.1)
Mycobacterium intracellulare	252 (35.4)
Mycobacterium abssessus complex	
Mycobacterium abscessus	93 (13.0)
Mycobacterium bolletii	53 (7.4)
Mycobacterium fortuitum	28 (3.9)
Mycobacterium gordonae	19 (2.7)
Mycobacterium kansasii	18 (2.5)
Total	**713 (100.0)**

2. Rare NTM isolated during the study period

During the study period, 90 NTM from 84 patients were identified as

rare NTM. *M. peregrinum* was the most common (17 specimens, 18.9%) and *M. conceptionense* (9 specimens, 10.0%), *M. chelonae* (7 specimens, 7.8%), *M. lentiflavum* (7 specimens, 7.8%), and *M. mageritense* (7 specimens, 7.8%) were also common. Rare NTM were isolated only once in 79 of 84 patients, twice from 4 patients, and three times from 1 patient (Table 2).

Table 2. Rare NTM species isolated from respiratory specimens

Identification	**Numbers (%)**
Mycobacterium peregrinum	17 (18.9)
Mycobacterium conceptionense	9 (10.0)
Mycobacterium chelonae	7 (7.8)
Mycobacterium lentiflavum	7 (7.8)
Mycobacterium mageritense	7 (7.8)
Mycobacterium chimaera	6 (6.8)
Mycobacterium terrae	5 (5.6)
Mycobacterium kumamotonense	4 (4.4)
Mycobacterium porcinum	3 (3.3)
Mycobacterium goodii	2 (2.2)
Mycobacterium nebraskens	2 (2.2)
Mycobacterium phocaicum	2 (2.2)
Mycobacterium septicum	2 (2.2)
Mycobacterium celatum	1 (1.1)
Mycobacterium holsaticum	1 (1.1)
Mycobacterium senuense	1 (1.1)
Mycobacterium arupense	1 (1.1)
Mycobacterium kubicae	1 (1.1)
Mycobacterium neoaurum	1 (1.1)
Mycobacterium xenopi	1 (1.1)
Unclassfiable	10 (11.1)
Total	**90 (100.0)**

M. phocaicum and *M. mageritense* were isolated in one patient, *M. peregrinum* and *M. concetionense* were isolated in one patient, and *M.*

chimaera was isolated three times in one patient.

3. Characteristics of 84 patients in whom rare NTM were isolated

The median age of 84 patients in whom rare NTM were isolated was 64 years (range, 26-84 years), and 50 (59.5%) of them were male. Twenty-eight (56.0%) patients had a past history of TB treatment. The most common underlying diseases were solid organ malignancies, including lung cancer (12 patients, 14.3%) and diabetes mellitus (8 patients, 9.5%). Sputum (46 patients, 54.8%) and cough (40 patients, 47.6%) were the most common symptom complaints. Postnasal drip (10 patients, 11.9%) and crackles (6 patients, 7.1%) were the most common findings of physical examination (Table 3).

Table 3. Demographic and clinical characteristics of 84 patients from whom rare NTM were isolated

Demographics	**N (%) /**
Age (year), median (range)	64.0 (26.0-84.0)
Sex (Male)	50 (59.5)
Body Mass Index (kg/m^2) ,median (range)	22.5 (14.8-29.0)
Habitual factors	**N (%)**
Smoking	24 (33.8)
Ex-smoker	16 / 71(22.5)
Current smoker	8 / 71 (11.3)
Past medical history	**N (%)**
Past history of TB	28 (56.0)
Measles	3 (13.0)
Pertussis	1 (4.3)
Sinusitis	5 (20)
Comorbidities	**N (%)**
Malignancies	12 (14.3)
Lung cancer	2 (2.4)

Diabetes	8 (9.5)
Cerebrovascular disease	2 (2.4)
Rheumatologic disease	3 (3.6)
Inflammatory bowel disease	1 (1.2)
Gastroesophageal reflux	1 (1.2)
Underlying lung disease	
COPD	5 (6.0)
Asthma	4 (4.8)
TB destroyed lung	4 (4.8)
ILD	1 (1.2)
Bronchiectasis	27 (32.1)
Symptoms	**N (%)**
Cough	40 (47.6)
Dyspnea	15 (17.9)
Hemoptysis	11 (13.1)
Sputum	46 (54.8)
Fever	6 (7.1)
Myalgia	5 (6.0)
Weight loss	7 (8.3)
Physical examination	**N (%)**
Post nasal drip	10 (11.9)
Crackle	6 (7.1)
Wheezing	1 (1.2)
Murmur	0 (-)
Clubbing	0 (-)
Peripheral edema	0 (-)

Upper lobes were commonly involved (right upper lobe in 46 patients and left upper lobe in 40 patients). Bilateral lesions were found in 36 patients (42.9%). In 24 (28.6%) patients, three or more lobes were involved in lesions. Multiple nodules were the most commonly observed radiographic findings (49 patients, 58.3%). Bronchiectasis (27 patients, 32.1%) and cavities (16 patients, 19.0%) were also commonly found in radiographic examinations (Table 4).

Table 4. Radiologic findings of 84 patients with rare NTM

Radiological findings	N (%)
Locations of the lesions	
Right upper lobe	46 (54.8)
Right middle lobe	26 (31.0)
Right lower lobe	28 (33.3)
Left upper lobe	40 (47.6)
Left lower lobe	26 (31.0)
Distribution of lesions	
Bilateral	36 (42.9)
Multilobular (≥3 lobes with abnormalities)	24 (28.6)
Characteristics of lesions	
Multiple nodules	49 (58.3)
Bronchiectasis	27 (32.1)
Cavity	16 (19.0)
Unilateral	11 (13.1)
Bilateral	5 (5.9)
Radiographic classification	
Upper lobe cavitary pattern	15 (17.9)
Nodular bronchiectatic pattern	18 (21.4)
Unclassifiable	51 (60.7)

4. Clinical course of five patients in whom rare NTM were isolated more than once

Five patients in whom rare NTM were isolated twice or more were followed up for a median duration of 396 days (range, 294-737 days). Initial chest CT showed bronchiectasis, small nodules, and consolidation (Figure 1). In one patient (patient 2 in Table 5) in whom rare NTM as well as *M. abscessus* were isolated, respiratory symptoms were aggravated and radiographic lesions progressed on follow-up

chest CT. The clinician who managed this patient judged that the progression was caused by *M. abscessus* rather than *M. goodie*. Subsequently, a clarithromycin-based regimen was started in this patient. In the other three patients (patients 1, 3, and 4 in Table 5), neither aggravation of symptoms nor progression of radiography lesions on chest radiography occurred. They had been observed without anti-NTM treatment. The other patient in whom *M. chimaera* were isolated three times (patient 5 in Table 5) developed new centrilobular nodules. However, the symptoms of this patient did not change (Table 5).

Table 5. Clinical characteristics of five patients in whom rare NTM were isolated more than once

Patients (sex/age)	Chief complaint	Underlying diseases	CT finding	Isolated NTM (time)	Duration of follow up (days)	Progression of radiographic lesions	Treatment (Y/N)
1 (F/74)	Sputum	● Hypertension ● History of tuberculous cervical lymphadenitis (anti-tuberculosis therapy, May. 2005-Oct. 2006)	● Tiny benign looking nodule in RUL apex ● Subsegmental atelectasis in LUL and RLL	*M. conceptionense* (2)	477	● Not definite	No
2 (F/33)	Cough Sputum Weight loss	● On jejunostomy state (due to lye ingestion) ● History of recurrent pneumonia ● Bipolar I disorder	● Multifocal consolidation with branching opacities in both lung	*M. abscessus*(2) *M. goodii* (2)	396	● Interval increase of multiple centrilobular nodules, bronchiectasis on chest CT	Yes Clarithromycin, Rifampin, Ethambutol, Moxifloxacin (Sep.2007-Oct.2009)
3 (F/63)	Blood tingled sputum Sputum	● Diabetes ● Coronary artery disease	● Bronchiectasis in the RML, LUL lingular infiltration in both lungs ● Calcified nodule in the RLL abbuting bronchiectasis	*M. phocaicum* (1) *M. mageritense* (1)	294	● Not definite	No
4 (F/53)	Cough Sputum	● No	● Bronchiectasis in RML, LUL lingular segment and LLL. ● Poorly defined centrilobular nodules with branching opacity in RUL anterior segment, RML, LUL lingular segment, LLL.	*M. peregrinum* (1) *M. conceptionense* (1)	737	● Not definite	No
5 (M/59)	Cough Hemoptysis	● History of pulmonary TB(20YA)	● About 7.3x5.1cm fluid containing cavity in RUL ● Multiple nodules, consolidation	*M. chimaera*(3)	378	● Newly appeared centrilobular nodules and patchy consolidation, LUL and RLL on chest CT	No

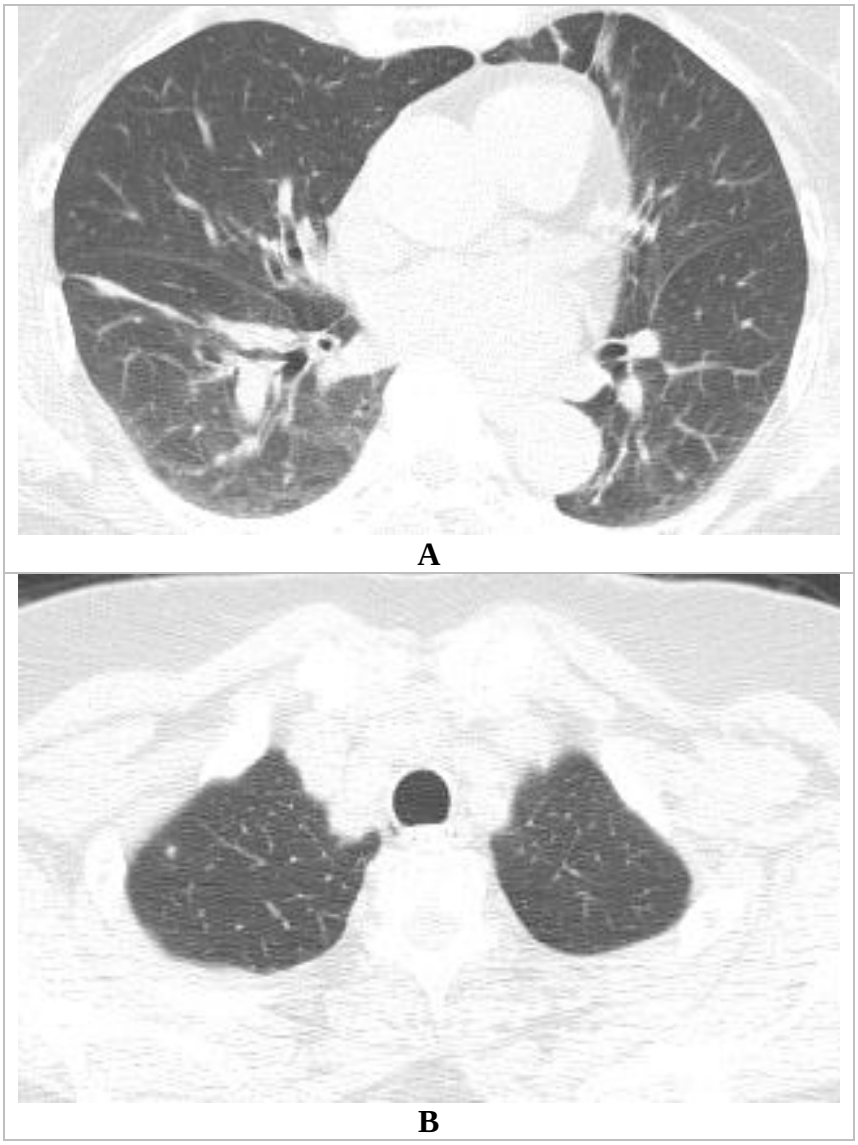
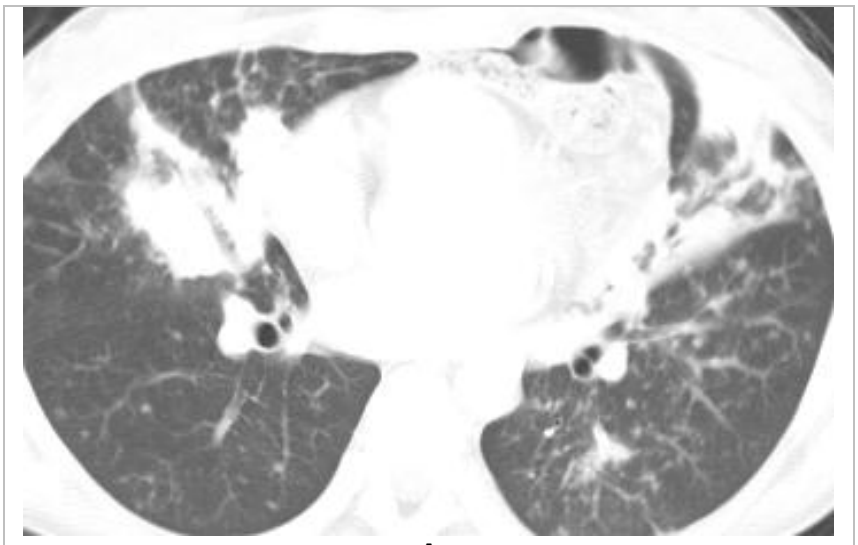


Figure 1. Chest computed tomography (CT) findings of patient No.1 in whom rare NTM of *M. conceptionense* were isolated twice.

Initial chest CT showed subsegmental atelectasis in the right lower lobe (A) and tiny nodule in right upper lobe apex (B).



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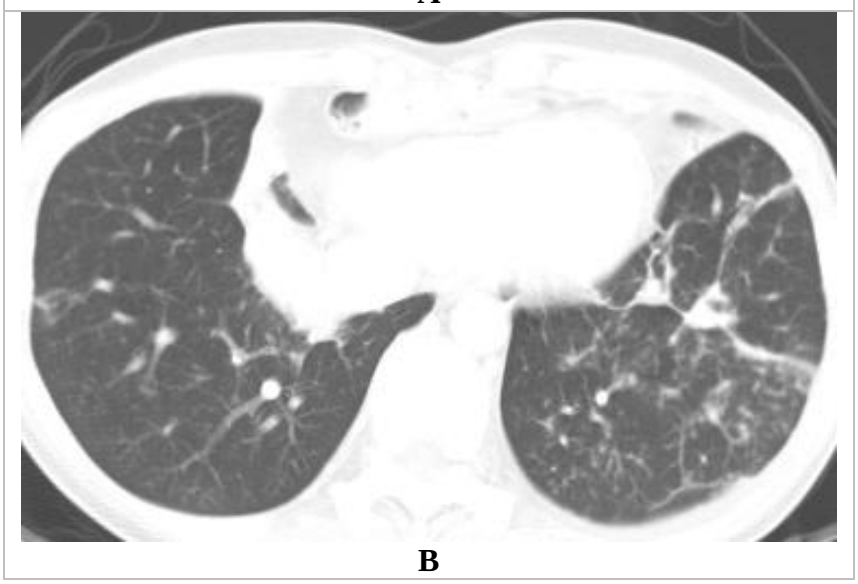

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Figure 2. Chest CT findings of patient No.2 in whom rare NTM of *M. goodii* and *M. abscessus* were isolated twice.

Chest CT revealed consolidations in the right middle lobe and lingular segment of the left upper lobe (A) and bronchiolitis in the left lower lobe (B).

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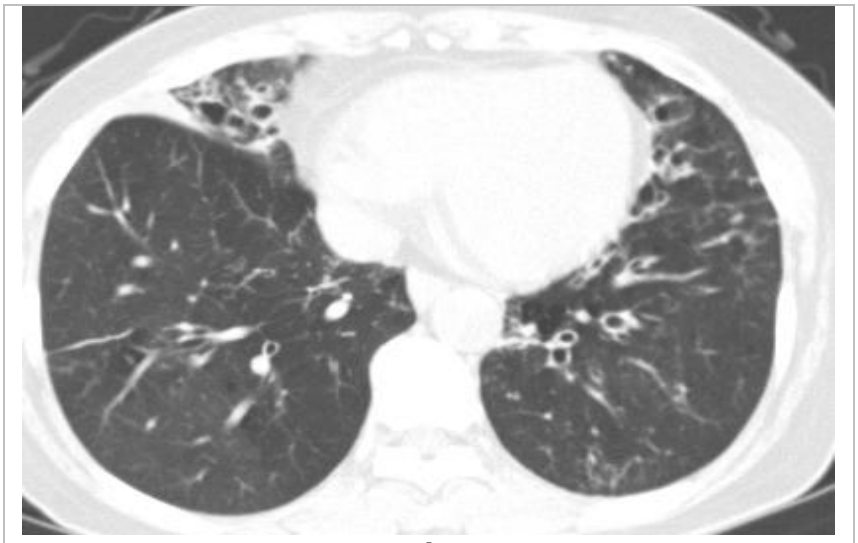

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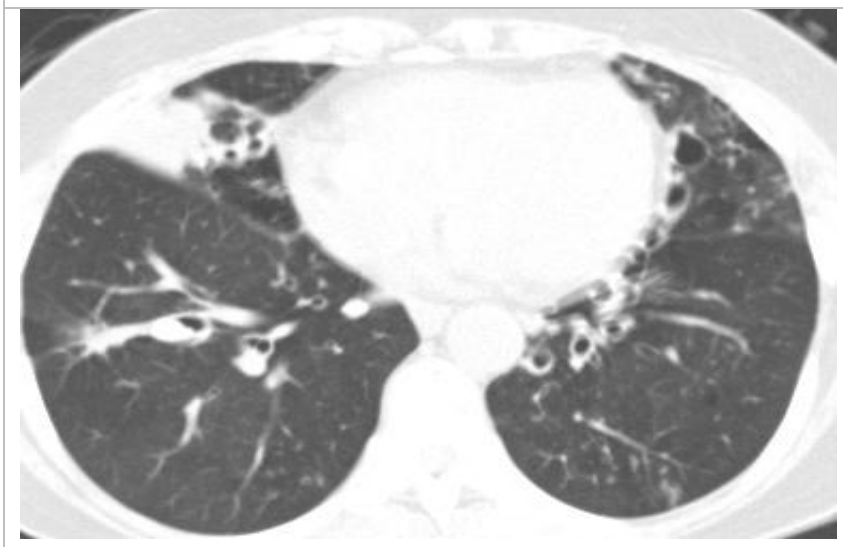

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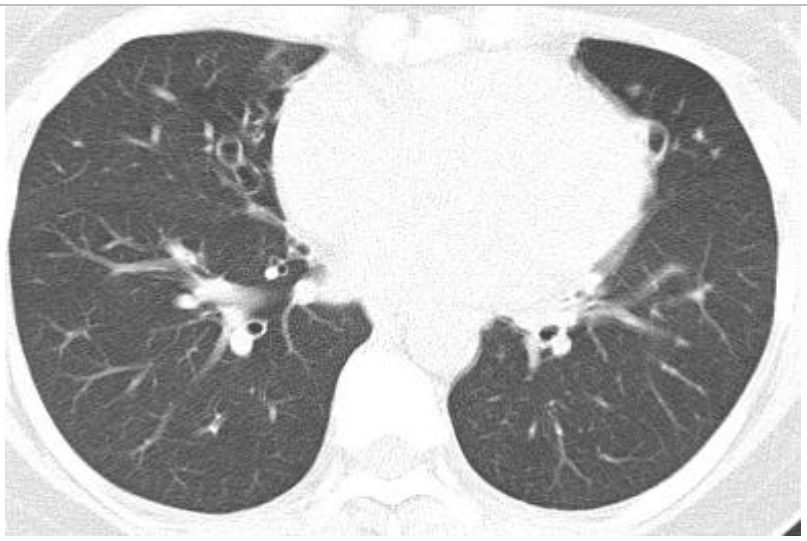
Figure 3. Chest CT findings of patient No.3 in whom rare NTM of *M. phocaicum* and *M.mageritense* were isolated.

Chest CT obtained bronchiectasis in the right middle lobe and lingular segment of the left upper lobe (A and B).



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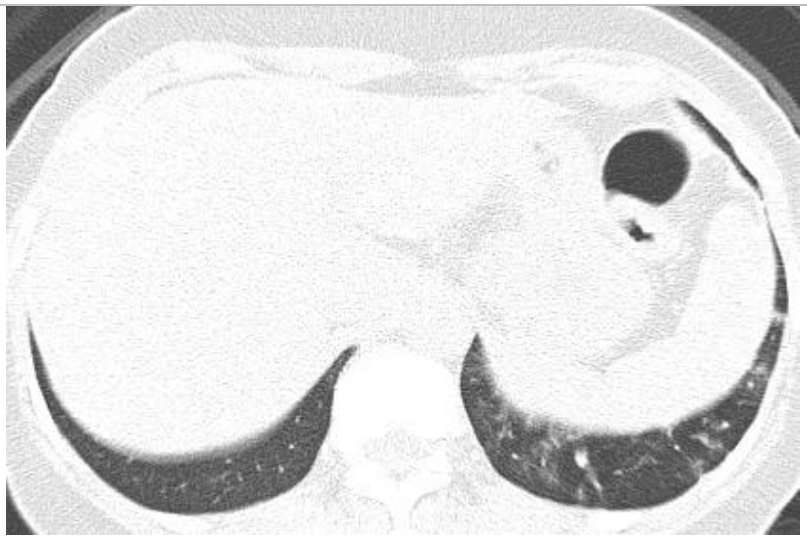
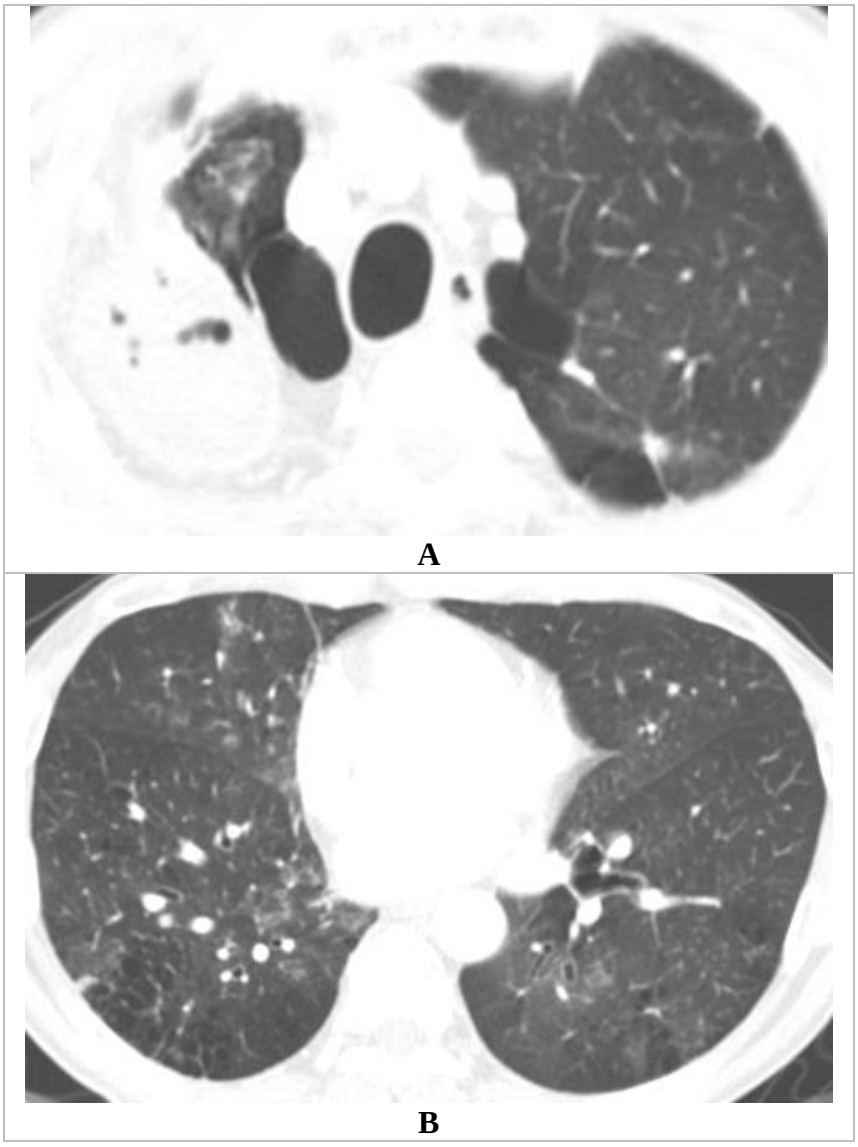


B

Figure 4. Chest CT findings of patient No.4 in whom rare NTM of *M. peregrinum* and *M. conceptionense* were isolated.

Initial CT showed bronchiectasis in the right middle lobe and lingular segment of the left upper lobe (A) and centrilobular nodules in the left lower lobe (B).



A

B

Figure 5. Chest CT findings of patient No.5 in whom rare NTM of *M. chimaera* were isolated three times.

Chest CT revealed a cavity of about 7.3x5.1 size containing fluid in the right upper lobe (A) and bilateral multiple small nodules (A and B).

DISCUSSION

Newly identified NTM have continuously been reported. In addition, the NTM lung diseases from those new organisms have also been continuously reported (27-30). In the present study, we elucidated that rare NTM was isolated only once most cases. Among 79 of 84 patients in whom rare NTM were identified, rare NTM were isolated only once. One-time isolation of most of the rare NTM suggests limited clinical significance of rare NTM.

M. peregrinum, which belongs to *M. fortuitum* group of rapidly growing NTM, was the most frequently isolated rare NTM in a present study (31). *M. peregrinum* is reported to cause infections of various organs such as the lungs and skin or of wounds among both immunocompetent and immunocompromised patients (32, 33).

Other rare NTM species isolated from patients in the present study (*M. conceptionense, M. lentiflavum, M. mageritense, and M. chimaera*) may also cause lung diseases (27, 29, 30). Other rare NTM isolated from the patients in the present study, such as *M. kumamotonense* and *M. celatum*, are generally considered misidentification or contamination of culture, and are thus deemed to be clinically nonpathogenic organisms (34, 35).

NTM lung disease is known to occur predominantly in women (36, 37). In contrast, rare NTM were isolated more frequently among males (60.0%) in the present study.

In addition, more than half of patients (64.0%) with rare NTM had a past history of pulmonary TB and 34 patients (40.5%) had underlying lung disease including bronchiectasis(27 patients, 32.1%), COPD(5 patients, 6.0%), and asthma(4 patients, 4.8%). Although rare NTM were frequently found in elderly men with a history of TB or underlying lung disease, radiographic lesions showing an upper lobe cavitary pattern was not common (15 patients, 17.9%) in the present study.

Among five patients in whom rare NTM were isolated more than once, only two showed evidence of radiographic aggravation with isolation of rare NTM.

In the first patient, *M. chimaera* was isolated three times although this species is generally considered to have limited pathogenicity. One study reported that none of the eight patients who were infected with *M. chimera* fulfilled the ATS criteria for NTM lung disease (38, 39). However, the patients in our study could be considered to have lung disease caused by *M. chimaera* because the organism was isolated three times and radiographic aggravation was observed with the isolation. In fact, lung disease caused by *M. chimaera* has been reported in a patient with cystic fibrosis or other underlying conditions including COPD (27, 40).

In the other patient, *M. goodii* was isolated twice; however, *M. abscessus* was also isolated twice before the isolation of *M.goodii*.

M. goodii was identified in 1999 as a rapidly growing NTM species related to the *M. smegmatis* (41). *M. goodii* has been associated with

infection of various sites such as sporadic cases of cellulitis and minor hospital outbreaks of surgical implants rather than pulmonary infection (42-44). Only a few cases have been reported with pulmonary manifestation concerning NTM infection induced by *M. goodie* (28). In this context, the causative NTM for the aggravation in this patient might be *M. abscessus* rather than *M. goodii*.

In case of patient 2 and 3, NTM were grown for two times, but the species of them were different. Physicians might concentrate on these patients who need clinical follow-up for symptoms, signs, microbiological sequence and chest images for deciding whether the infection was simple colonization or true infection which needed further evaluation. Finally, these two patients have been under follow-up at our institution.

CONCLUSIONS

Most of the rarely identified NTM species were identified only once in patients. In addition, clinical and radiographical aggravation were rarely observed in patients in whom rare NTM were isolated two or more times. In conclusion, rarely identified NTM have limited clinical importance. Clinicians who meet patients with rarely identified NTM should observe them closely without invasive work up.

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