Pulmonary Disease Caused by Rapidly Growing Mycobacteria: A Retrospective Study of 44 Cases in Japan

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Key Words

Mycobacterium chelonae • *Mycobacterium fortuitum* • Lung •
Mycobacterium abscessus • *Mycobacterium peregrinum* •
Rapidly growing mycobacteria

Abstract

Background: The features of pulmonary disease caused by rapidly growing mycobacteria (RGM) have not been sufficiently documented. **Objectives:** To establish these features, we retrospectively evaluated 44 patients. **Methods:** We screened respiratory isolates at the National Toneyama Hospital (Osaka, Japan) between 2003 and 2007. Diagnosis was based on the latest guidelines of the American Thoracic Society. The patients were classified into 3 types according to their radiographic findings: fibrocavitary, nodular bronchiectatic and unclassified variant. **Results:** We obtained 1,348 nontuberculous mycobacteria respiratory isolates from 1,187 patients, including 119 RGM isolates from 100 patients. Forty-four of these 100 patients were definitively diagnosed with respiratory disease due to RGM. The most common pathogen was *Mycobacterium abscessus*, which accounted for 65.9% of cases, followed by *Mycobacterium fortuitum* at 20.5%. There was a statistically significant differ-

ence in smoking history between patients infected with these 4 RGM species (excluding those with an unknown smoking history; $p = 0.039$). The overall evaluation of radiographic findings revealed 18.2% as fibrocavitary, 43.2% as nodular bronchiectatic and 38.6% as unclassified variants in these 44 patients. There was a significant difference in radiographic findings between the 4 RGM species ($p = 0.002$). There was also a significant difference in radiographic findings between *M. abscessus* and *M. fortuitum* infected patients ($p = 0.022$). **Conclusions:** Patients with *M. abscessus* seem to have less of a smoking history and more frequent nodular bronchiectatic radiographic patterns than patients with *M. fortuitum*. In contrast, fibrocavitary patterns might be more frequent with *M. fortuitum* infection.

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Introduction

Nontuberculous mycobacteria (NTM) are ubiquitous organisms that are found in various environmental sources including water, dust and soil [1]. NTM have been widely recognized as important pathogens that may cause chronic pulmonary disease. Because the overall preva-

lence of pulmonary disease caused by tuberculosis is declining in Japan, the proportion of pulmonary disease caused by NTM is increasing [2]. The *Mycobacterium avium* complex (MAC) is the most common cause of pulmonary NTM disease; however, the other NTMs can also cause pulmonary disease [3].

Rapidly growing mycobacteria (RGM) belong to NTM and are the Runyon Group IV organisms that usually form colonies within 7 days of incubation, as opposed to slow-growing mycobacteria that require a longer incubation period [4]. RGM have been reported to cause pulmonary disease in humans [5, 6]. A report from the United States indicated that 10% of pulmonary NTM disease cases were due to RGM [7]. Griffith et al. [8] reported that 154 patients with pulmonary RGM disease in the United States were predominately white female non-smokers; upper lobe infiltrates were the most common radiographic findings, whereas cavitation was present in only 16%. A report from Gerogianni et al. [9] indicated that *M. fortuitum* was most frequently isolated as the NTM pathogen in Greece. In France, it was reported that 10.7% of pulmonary NTM disease was due to RGM [10]. The clinical features of pulmonary NTM disease in Korea were also reported, where *M. abscessus* was the second most commonly isolated pathogen in 195 cases [11]. A recent study reported that the high prevalence of RGM was a distinct characteristic of pulmonary NTM disease in Asia [12].

The clinical features of pulmonary RGM disease in other regions, including Japan, have not been sufficiently explored. To gain further insights into pulmonary RGM disease, notably in Japan, we retrospectively evaluated the clinical and radiographic features of 44 patients with pulmonary RGM disease during a 4-year period in our institution, which is the third largest specialist hospital for respiratory diseases in Osaka. The RGM species that we identified from patients studied included *M. abscessus*, *M. fortuitum*, *M. chelonae* and *M. peregrinum*.

Patients and Methods

Study Population and Diagnostic Criteria

Cases of pulmonary disease caused by RGM were identified from respiratory isolates obtained from the microbiology laboratory at the National Toneyama Hospital between October 2003 and December 2007. Nonrespiratory isolates such as gastric fluids were excluded. The diagnosis of pulmonary RGM disease was based on the latest guidelines of the American Thoracic Society (ATS) [5], which specify clinical and microbiologi-

cal criteria for diagnosing pulmonary NTM disease. Briefly, the clinical criteria consist of having respiratory symptoms, characteristic nodular or cavitary opacities on chest radiographs or multifocal bronchiectasis with multiple small nodules shown by high-resolution CT scans, and the appropriate exclusion of other diseases. The microbiological criteria needed positive culture results from at least two separate expectorated sputum samples or a positive culture result from at least one bronchial wash or lavage.

Identification of RGM Species

RGM species were identified using DNA-DNA Hybridization Mycobacteria 'Kyokuto' Kits (Kyokuto Pharmaceuticals, Tokyo, Japan) [13]. Briefly, DNA was extracted from clinical isolates and labeled with photoreactive biotin and then distributed into the wells of a microdilution plate in which reference DNA samples had been previously immobilized. After hybridization, the DNA was quantitatively detected with peroxidase-conjugated streptavidin and the substrate tetramethylbenzidine. With this DNA-DNA hybridization method, we can distinguish 17 species of NTM including the RGM species, *M. abscessus*, *M. fortuitum*, *M. chelonae* and *M. peregrinum* [13].

Evaluation of Pulmonary RGM Disease

The medical records of the patients with a confirmed diagnosis of pulmonary RGM disease were reviewed retrospectively, including the following information: observation period, age, gender, body mass index, smoking history, respiratory symptoms, previous mycobacterial disease, and previous pulmonary diseases. Chest radiographs and CT scans were reviewed by two pulmonologists. Radiographic findings were evaluated with regard to the presence or absence of nodules, cavity lesions and bronchiectasis.

The patients with pulmonary RGM disease were divided into 3 types according to the radiographic findings: fibrocavitary, nodular bronchiectatic and unclassified variant. Representative images of each pattern are presented in figures 1 and 2. The classification of these patterns was determined with reference to the latest guidelines of the ATS [5] and a few recent reviews of pulmonary NTM disease in the literature [14, 15]. Due to the underlying pulmonary disease, some patients have architectural distortions on chest radiographic findings. If the pulmonologist found it difficult to assign an accurate classification, these patients were assessed as having the unclassified variant pattern.

The study was approved by the National Toneyama Hospital Institutional Review Board. This approval allowed for retrospective chart review and anonymous results reporting without informed consent.

Statistical Analysis

Variables were expressed as means with standard deviations. Categorical values were expressed as numbers and percentages. Comparisons were performed using the Kruskal-Wallis test for continuous variables and Fisher's exact test for categorical variables. All comparisons were performed with SPSS 19 software (SPSS Inc., Chicago, Ill, USA). A p value <0.05 was considered to indicate a significant difference.

Fig. 1. Pulmonary disease caused by *M. abscessus* in a 61-year-old woman. **a** Chest radiograph showing reticulonodular lesions in the bilateral middle and lower lung field (arrows). **b** Chest CT scan showing centrilobular nodules, lobular consolidation and bronchiectasis (arrows). We classified patients with these radiographic findings as having nodular bronchiectatic patterns.

Fig. 2. Pulmonary disease caused by *M. fortuitum* in a 48-year-old man. **a** Chest radiograph showing a cavity lesion in the left upper lung field (arrows) and pleural thickenings and calcifications in the peripheral left lung field. **b** Chest CT scan showing a cavitory lesion and pleural thickenings in the left upper lobe (arrow). Also note volume loss of the left lung due to pleural thickenings and calcifications. We classified patients with these radiographic findings as having fibrocavitory patterns.

Table 1. Frequency of patients with pulmonary disease caused by RGM

Organism	Patients from whom RGM were isolated (A)	Patients who met the criteria for diagnosis (B)	Ratio B/A %
<i>M. abscessus</i>	49	29	59.2
<i>M. fortuitum</i>	33	9	27.3
<i>M. chelonae</i>	9	4	44.4
<i>M. peregrinum</i>	9	2	22.2
RGM	100	44	44

Table 2. Clinical and radiographic characteristics of patients with pulmonary disease caused by RGM

	RGM (n = 44)	<i>M. abscessus</i> (n = 29)	<i>M. fortuitum</i> (n = 9)	<i>M. chelonae</i> (n = 4)	<i>M. peregrinum</i> (n = 2)	p value
Gender, male/female	22/22	11/18	6/3	3/1	2/0	0.140 ^a
Age, years	68.8 ± 14.2	68 ± 16.1	67.4 ± 10.1	75.3 ± 8.6	74.0 ± 14.1	0.671 ^b
BMI	18.7 ± 2.6	18.9 ± 2.7	17.7 ± 2.4	19.2 ± 3.6	19.4 ± 0.4	0.799 ^b
Smoking history: ever/never/unknown	10/27/7	4/22/3 ^d	4/4/1 ^d	1/0/3 ^d	1/1/0 ^d	0.006 ^{a, d}
Respiratory symptoms						
Cough	20 (45.5)	15 (51.7)	4 (44.4)	0	1 (50.0)	0.269 ^a
Sputum/hemosputum	22 (50.0)	17 (58.6)	4 (44.4)	0	1 (50.0)	0.165 ^a
Observation period, months	34.3 ± 31.1	38.6 ± 34.7	24.2 ± 12.8	39 ± 34.1	7.0 ± 1.4	0.169 ^b
Underlying pulmonary disease						
Cured tuberculosis	19 (43.2)	11 (37.9)	4 (44.4)	3 (75.0)	1 (50.0)	0.616 ^a
Pulmonary NTM, excluding RGM	8 (18.2)	6 (20.7)	2 (22.2)	0	0	1.000 ^a
Disease not caused by mycobacteria	10 (22.7)	7 (24.1)	2 (22.2)	0	1 (50.0)	0.613 ^a
Radiographic findings						
Fibrocavitary pattern	8 (18.2)	3 (10.3) ^c	5 (55.6) ^c	0	0	
Nodular bronchiectatic pattern	19 (43.2)	16 (55.2) ^c	3 (33.3) ^c	0	0	0.002 ^a
Unclassified variant pattern	17 (38.6)	10 (34.5) ^c	1 (11.1) ^c	4 (100)	2 (100)	

Data are presented as numbers with percentages in parentheses, or the mean ± SD.

^a Fisher's exact test. ^b Kruskal-Wallis test. ^c Statistically significant difference between *M. abscessus* and *M. fortuitum* (p = 0.022), using Fisher's exact test. ^d Statistically significant difference between patients with 4 RGM species excluding those with unknown smoking history (p = 0.039), using Fisher's exact test.

Results

Patient Population

We obtained 1,348 NTM respiratory isolates from 1,187 patients from 2003 to 2007 (multiple samples from some patients). Of the 1,348 NTM isolates, 911 from 790 patients were MAC, 88 from 78 patients were *M. kansasii*, and 119 from 100 patients were RGM isolates. In these latter 100 patients, *M. abscessus*, *M. fortuitum*, *M. chelonae* and *M. peregrinum* were found in 49, 33, 9 and 9 patients, respectively, and 44% were diagnosed with pulmonary RGM disease based on the criteria previously described.

The diagnosis of pulmonary disease was confirmed in 59.2% of *M. abscessus* (29 of 49), 27.3% of *M. fortuitum* (9 of 33), 44.4% of *M. chelonae* (4 of 9), and 22.2% of *M. peregrinum* infections (2 of 9). Hence, *M. abscessus* accounted for 65.9% (29 of 44) of patients with pulmonary RGM disease and was thus the most common isolate from patients with respiratory disease due to RGM (table 1).

Clinical and Radiographic Characteristics of Patients with Pulmonary RGM Disease

The clinical and radiographic characteristics of patients with pulmonary RGM disease are summarized in

table 2. Their mean age was 68.8 ± 14.2 years, mean observation period 34.3 months (range 2–157), male:female ratio 50:50, and their a mean body mass index 18.7 ± 2.6 . Twenty patients (45.5%) had a cough at diagnosis, and 22 (50.0%) had sputum or hemospotum. Twenty-seven patients (61.4%) were non-smokers. Nineteen (43.2%) had a previous history of pulmonary tuberculosis, while 8 (18.2%) had a previous history of pulmonary NTM disease, excluding RGM. Ten patients (22.7%) had pulmonary disease not associated with mycobacteria. Females accounted for 62.1% of patients with *M. abscessus* and 75.9% were non-smokers, whereas males accounted for 66.7% of patients with *M. fortuitum* and 44.4% had a smoking history. We observed no statistically significant differences in any of these characteristics except for smoking history between patients with 1 of the 4 RGM species. However, there was a statistically significant difference in smoking history between the patients infected with any of the 4 RGM species when those with an unknown smoking history were excluded ($p = 0.039$).

All 44 patients with pulmonary RGM disease underwent X-ray examination and 35 (79.5%) received a chest CT scan. Eight (18.2%) were classified as having fibrocavitary patterns according to their radiographic findings, 19 (43.2%) had nodular bronchiectatic patterns, and 17 (38.6%) were unclassifiable. None of the patients with pulmonary disease caused by *M. chelonae* or *M. peregrinum* could be classified. There was a significant difference in radiographic findings between the 4 RGM species ($p = 0.002$). Among the 29 patients with *M. abscessus*, 55.2% had nodular bronchiectatic patterns, while 10.3 and 34.5% had fibrocavitary and unclassified variant patterns, respectively. On the other hand, among the 9 patients with *M. fortuitum*, 55.6% had fibrocavitary patterns, while 33.3 and 11.1% had nodular bronchiectatic and unclassified variant patterns, respectively. There was also a significant difference in radiographic findings between *M. abscessus* and *M. fortuitum* infected patients ($p = 0.022$).

Discussion

The clinical features and radiographic manifestations of pulmonary RGM disease are relatively undefined. To the best of our knowledge, the present study is the first to describe the clinical features of pulmonary RGM disease in Japan. Furthermore, we also described the differences between RGM species in terms of disease characteristics. First, patients with *M. abscessus* seem to have less of a

smoking history than patients infected with the 3 other RGM species. Second, according to radiographic findings, nodular bronchiectatic patterns might be more frequently observed with *M. abscessus* than with *M. fortuitum*, whereas fibrocavitary patterns seem more frequent with *M. fortuitum*. These differences had not been clearly described in previous reports.

For the past decade, the ATS diagnostic criteria of NTM lung disease have changed. The diagnostic rate may increase and time to diagnosis may shorten [16]. The diagnosis of pulmonary RGM disease in the present study was based on the latest guidelines of the ATS. According to the data in table 2, approximately half (43.2%) of the patients with pulmonary RGM disease had a history of cured tuberculosis and 18.2% of the patients had pulmonary disease with NTM, excluding RGM. More than half of the patients with pulmonary RGM disease had a history of other pulmonary mycobacterial infection. The mechanism of susceptibility to repeated mycobacterial infection has been investigated with some aspect of host factors in the patients with no immunodeficiency. Local dysfunction of the immune system may occur due to destruction of airway wall in the patients with preexisting pulmonary disease. On the other hand, the genetic factors may play a role in the development of pulmonary NTM disease in the patients without underlying pulmonary disease. The cystic fibrosis transmembrane conductance regulator gene and the natural resistance-associated macrophage protein 1 gene are reported as those genetic factors [17, 18]. Approximately 50% of patients with pulmonary RGM disease in the present study had respiratory symptoms and no smoking history. Most of these results are concordant with the results in previous reports [5, 8, 19]. *M. abscessus* was found in 65% of pulmonary RGM disease, and the ratio of patients who met the diagnostic criteria to patients from whom RGM was isolated was highest in those patients with *M. abscessus*. This result also coincided with the results of previous reports in which *M. abscessus* was found to be the most virulent pathogen in pulmonary RGM disease [5, 8, 11, 19]. The patients in the present study were lean, aged and did not show any sex bias. However, there was a trend towards female dominance at least for *M. abscessus* infection, with 62.1% being women. With respect to the ratio of patients from whom RGM was isolated to the patients who met the criteria for diagnosis, 59.4 and 27.3% of patients with *M. abscessus* and *M. fortuitum*, respectively, were diagnosed with pulmonary NTM disease in the present study (table 1). Only 45.4 and 9.7% of patients with *M. abscessus* and *M. fortuitum* complex were diagnosed with pulmo-

nary RGM disease in a Korean report [11]. These results of both the Korean and the present Japanese study indicate that a substantial proportion of the RGM isolates from respiratory specimens were considered to be colonizations or contaminations.

In general, the features of the radiographic findings in patients with pulmonary NTM disease were classified based on the following patterns: cavitary pulmonary disease, involving the upper lobes of middle-aged men with a history of smoking, usually having underlying pulmonary disease, and nodular bronchiectasis generally affecting elderly non-smoking women without underlying pulmonary disease. In addition, solitary pulmonary nodules and hypersensitivity pneumonitis patterns were also observed in a few patients [5, 14, 15]. In a study of 12 patients with *M. abscessus*, the main radiographic findings were bilateral small nodular opacities, bronchiectasis and cavity formation [20]. In this study, a nodular bronchiectatic pattern was observed in 7 patients (58.3%), while upper lobe cavitary patterns were seen in 5 patients (41.7%). CT findings in 14 patients with *M. chelonae* revealed that the major features were diffuse bronchiectasis, multiple nodules, consolidation and less cavitation, i.e. resembling those of MAC [21]. One report described that cavitation was unusual and occurred in <20% of cases with RGM [8]. The differences in CT features between MAC and pulmonary RGM disease have been investigated in two other studies [22, 23]. Chung et al. [22] reported no significant differences between MAC and *M. abscessus* in terms of the presence of small nodules, tree-in-bud appearance and bronchiectasis; however, lobar volume loss, nodules, consolidation and thin wall cavities were more frequently seen in MAC than in *M. abscessus* infections [22]. The upper lobe cavitary pattern was more frequent with MAC (37%) than with *M. abscessus* (14%), whereas the nodular bronchiectatic pattern was more common with *M. abscessus* (81%) than with MAC (53%) [22]. The other study compared CT features of pulmonary NTM disease including that caused by MAC, *M. fortuitum* and *M. chelonae*. Bronchiectasis and nodules were significantly more frequent and severe in patients with MAC than in those with *M. fortuitum* or *M. chelonae* [23]. Therefore, on the basis of these two studies, it is speculated that nodular bronchiectatic patterns may be more frequent with *M. abscessus* than with *M. fortuitum* or *M. chelonae* infection. In fact, nodular bronchiectatic patterns were found in 55.2% of patients with *M. abscessus*, but only in 33.3% with *M. fortuitum* in the present study. These radiographic features appear to be in accordance with the above notion; to date, few reports have clearly

described these differences. We also suggest that patients with *M. abscessus* might have less of a smoking history than patients infected with the other 3 RGM species. Thus, the major characteristics of patients with *M. abscessus* are thought to be a minor smoking history and more nodular bronchiectasis in radiographic findings compared to the other RGM species. This agrees with previous reports in which nodular bronchiectasis generally affected elderly non-smoking women without underlying pulmonary disease [5, 14, 15]. However, the mechanism responsible for the difference between a minor smoking habit and nodular bronchiectasis in radiographic findings is unknown.

The present study has several limitations. First, we could not complete the smoking history review in 7 of 44 patients (15.9%) with pulmonary RGM disease. Therefore, the result with regard to smoking history may be incomplete. If complete data could have been obtained, we might have come to the conclusion that smoking history makes no difference to the type of infection in pulmonary RGM disease. Second, the sample size of patients infected with certain RGM species in the present study was very small, especially for *M. chelonae* and *M. peregrinum*. No fibrocavitary and nodular bronchiectatic patterns were observed in patients infected with those RGM species. We conducted a statistical analysis not only for the 4 RGM species but also for *M. abscessus* and *M. fortuitum* because of the small sample size for *M. chelonae* and *M. peregrinum*. Analysis of a larger sample might result in different conclusion.

In conclusion, we described the clinical and radiographic features of pulmonary RGM disease in Japan, as well as the differences between RGM species infection: patients with *M. abscessus* seem to have less of a smoking history and more frequent nodular bronchiectatic radiographic patterns than patients with *M. fortuitum*. In contrast, fibrocavitary patterns might be more frequent with *M. fortuitum* infection. However, given its retrospective design and small number of patients, the present study had limitations which reduce the robustness of the conclusions. Further studies are warranted to confirm the results of the present pilot study.

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