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Isolation of nontuberculous mycobacteria from patients with pneumoconiosis

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Abstract This study aimed to confirm the isolation of nontuberculous mycobacteria (NTM) from patients with pneumoconiosis. Monthly sputum examinations in 155 patients were performed from April 1998 to December 2002. When NTM were isolated, species were identified and the frequency of isolation was reviewed. We then identified the patients who satisfied the bacteriologic criteria for the diagnosis of nontuberculous mycobacterial pulmonary disease (NTM pulmonary disease) recommended by the American Thoracic Society (ATS). Symptoms and findings on computed tomography (CT) scans were evaluated. NTM were isolated from 60 patients (39%): common etiologic species defined by the ATS, i.e., *Mycobacterium avium*, *M. intracellulare*, *M. abscessus*, and *M. kansasii*, were identified in 21 patients; unusual etiologic species, i.e., *M. fortuitum*, *M. simiae*, and *M. szulgai*, were identified in 11 patients; and undefined species, which appeared to be nonpathogenic, were identified in 41 patients. The bacteriologic criteria were satisfied in 8 patients. NTM species isolated in conformity with the bacteriologic criteria were: *M. avium* in 4 patients, *M. intracellulare* in 2, a combination of *M. intracellulare* and *M. kansasii* in 1, and *M. gordonae* in 1 patient. Two patients, from whom *M. avium* were repeatedly isolated, satisfied the ATS diagnostic criteria for NTM pulmonary disease. It is important to note that NTM, including both pathogenic species and nonpathogenic species, were isolated from patients with pneumoconiosis.

Key words Nontuberculous mycobacteria · Pneumoconiosis

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Introduction

It is well known that pulmonary tuberculosis is commonly associated with pneumoconiosis.[1,2] Recently, nontuberculous mycobacterial pulmonary disease (NTM pulmonary disease) in patients with pneumoconiosis has also been reported.[3–6]

The American Thoracic Society (ATS) recommended diagnostic criteria for NTM pulmonary disease in 1997.[7] All three sets of criteria (clinical, radiographic, and bacteriologic) must be satisfied in patients from whom nontuberculous mycobacteria (NTM) are isolated in order to make a diagnosis of NTM pulmonary disease. In some patients with pneumoconiosis, however, it is difficult to decide whether the clinical criteria are satisfied, because of pre-existing symptoms.[7] The same may be true of the radiographic criteria. Thus, bacteriologic findings should be evaluated carefully in patients with pneumoconiosis.

This study aimed to confirm the isolation of NTM from patients with pneumoconiosis, and to suggest some points which could be important in the followup of pneumoconiosis.

Patients and methods

The study population comprised 155 patients with pneumoconiosis at Asahi Rosai Hospital (136 men and 19 women; mean age, 70.6 years; age range, 53 to 87 years at the beginning of the study). Monthly sputum examinations were performed from April 1998 to December 2002.

When NTM were isolated, species were identified and the frequency of isolation was reviewed. We then identified the patients who satisfied the bacteriologic criteria for the diagnosis of NTM pulmonary disease recommended by the ATS. Changes in symptoms and in findings on computed tomography (CT) scans were evaluated. The patients' backgrounds were also investigated for the following factors: age at the beginning of the study, sex, risk factors for

tuberculosis (diabetes mellitus, history of gastrectomy, and use of corticosteroids),[8] history of occupational exposure to dust, and chest X-ray findings due to pneumoconiosis (size of large opacities and profusion of small opacities). A history of pulmonary tuberculosis was excluded from the investigation of their backgrounds, because antituberculous agents had been administered to some patients with pneumoconiosis from whom *Mycobacterium tuberculosis* were not isolated and in whom deterioration of the radiographic findings was observed.

The sputum was examined with Ziehl-Neelsen staining, and was cultured for mycobacteria, using 2% Ogawa egg medium (Kyokuto, Tokyo, Japan) for 8 weeks at 37°C. NTM species were identified by a microplate hybridization method with DDH Mycobacteria (Kyokuto). Chest X-ray findings due to pneumoconiosis were classified according to the guidelines of the International Labour Office.[9] Large opacities were classified into three categories: an opacity having a diameter exceeding 10 mm and up to 50 mm (category A); an opacity which was larger than that in category A whose area did not exceed the equivalent of the right upper zone (category B); and an opacity whose area exceeded the equivalent of the right upper zone (category C). Small opacities were classified into four categories (categories 0, 1, 2, and 3), which represented an increasing profusion of small opacities, as defined by the corresponding standard radiographs.[9]

Results

Of the 155 patients with pneumoconiosis in this study, 20 (13%) suffered from diabetes mellitus, 11 (7.1%) had a history of gastrectomy, and 12 (7.7%) had used corticosteroids. Histories of occupational exposure to dust were as follows: 97 worked in pottery, 27 in coal mining, 23 in tunneling, 10 in foundries, 9 in stone masonry, 7 in welding, 3 in construction work, 2 in gold mining, 2 in metal grinding, 1 in asbestos work, 1 in copper mining, 1 in the manufacture of glass, and 1 in the manufacture of coke (27 patients had two or more occupations in their history). As for chest X-ray findings due to pneumoconiosis, large opacities were found in 94 patients (61%): 6 were classified as category A, 68 as category B, and 20 as category C. It was possible to evaluate the profusion of small opacities in 142 patients (92%): 53 were classified as category 1, 64 as category 2, and 25 as category 3.

NTM were isolated from 60 (39%) of the 155 patients with pneumoconiosis (two or more species were isolated from 17 patients). Thirteen species were identified, including common etiologic species[7] (in 21 patients), unusual etiologic species (in 11 patients), and undefined species which were not classified as belonging to either of the former two groups (in 41 patients; Table 1).

Eight patients satisfied the bacteriologic criteria for the diagnosis of NTM pulmonary disease. NTM species isolated in conformity with the bacteriologic criteria were: *M. avium* in 4 patients, *M. intracellulare* in 2, a combination of *M. intracellulare* and *M. kansasii* in 1, and *M. gordonae* in 1 patient (Table 2).

Table 1. Species of nontuberculous mycobacteria isolated from the 60 patients with pneumoconiosis

	Number of patients[a]
Common etiologic species (n = 21)[b]	
Mycobacterium avium	18
M. intracellulare	3
M. abscessus	2
M. kansasii	1
Unusual etiologic species (n = 11)[b]	
M. fortuitum	8
M. simiae	2
M. szulgai	1
Undefined species (n = 41)[c]	
M. gordonae	17
M. terrae	12
M. nonchromogenicum	5
M. peregrinum	5
M. chelonae	5
M. scrofulaceum	1

[a] Two or more species were isolated from 17 patients
[b] Classification defined by the American Thoracic Society in 1997
[c] Species that were classified as neither common etiologic species nor unusual etiologic species

Nonspecific respiratory symptoms, such as cough, sputum, and dyspnea, were continuously observed in the eight patients. However, new symptoms appeared in two patients, who satisfied the clinical criteria (cases 1 and 2). Deterioration of findings on CT scans was observed in five patients, among whom the radiographic criteria were satisfied in 2 patients (cases 1 and 2); thus, all three diagnostic criteria for NTM pulmonary disease were satisfied in these two patients (cases 1 and 2). Linear shadows or the progression of massive shadows, findings which were not included in the radiographic criteria, were observed in three patients (cases 3, 5, and 6). The findings on CT scans of cases 1, 2, and 6 are shown in Fig. 1.

The backgrounds of the above eight patients were as follows: all were men; mean age was 68.4 years (age range, 62 to 82 years at the beginning of the study); one suffered from diabetes mellitus (case 2) and one had a history of gastrectomy (case 6). Five worked in pottery (cases 2, 3, 5, 6, and 7); three worked in tunneling (cases 1, 7, and 8); one worked in coal mining (case 4); one worked in welding (case 1); and one worked in gold mining (case 2). Large opacities were found in six patients; five were classified as category B (cases 2, 3, 5, 6, and 8) and one as category C (case 1). Profusion of small opacities was evaluated in all eight patients; one was classified as category 1 (case 2); five as category 2 (cases 3, 5, 6, 7, and 8); and two as category 3 (cases 1 and 4).

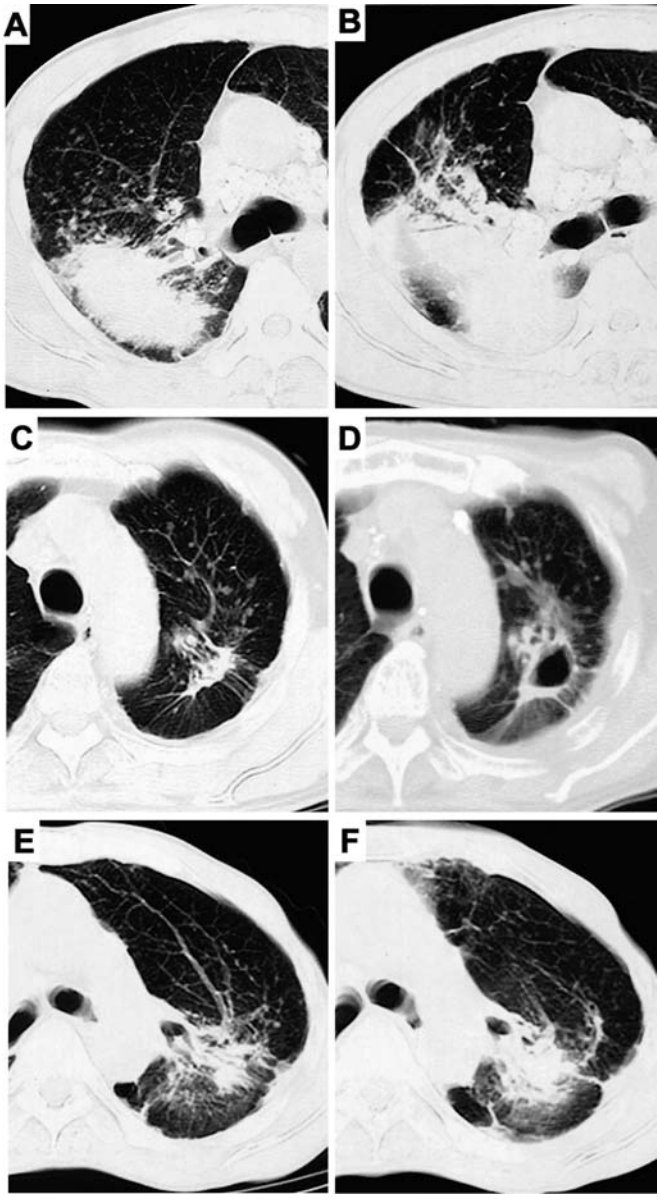
Discussion

There are several reports on studies of the relationship between NTM pulmonary disease and pneumoconiosis in

Table 2. Species of nontuberculous mycobacteria (NTM), symptoms, and findings on CT scans in the eight patients with pneumoconiosis who satisfied the bacteriologic criteria for the diagnosis of NTM pulmonary disease

Case no.	Age (years)[a]	Species[b]	Symptoms[c]	Findings on CT scan[d]
1	62	*M. avium*	Cough, sputum, dyspnea, fatigue, fever	Massive shadows, nodules, infiltrates
2	69	*M. avium*	Cough, sputum, hemoptysis	Massive shadows, nodules, cavity
3	69	*M. avium*	Cough, sputum	Massive shadows, nodules, linear shadows
4	68	*M. avium*	Cough, sputum, dyspnea	Nodules
5	82	*M. intracellulare*	Cough, sputum	Massive shadows, nodules, progression of massive shadows
6	64	*M. intracellulare*	Cough, sputum, dyspnea	Massive shadows, nodules, progression of massive shadows
7	69	*M. intracellulare* *M. kansasii*	Cough, sputum	Nodules
8	64	*M. gordonae*	Cough, sputum, dyspnea	Massive shadows, nodules

[a] Age at the beginning of the study
[b] Species isolated in conformity with the bacteriologic criteria for the diagnosis of nontuberculous mycobacterial pulmonary disease
[c] Symptoms newly observed in the observation period are underlined
[d] New findings or deterioration of findings on CT scans in the observation period are underlined



South African gold miners.[3–5] Sonnenberg et al.[3] compared risk factors in pulmonary tuberculosis and NTM pulmonary disease. Among patients with pulmonary tuberculosis, 0.7% (3/425) had chest X-ray findings consistent with pneumoconiosis, while among those with NTM pulmonary disease, the rate, of 5.9% (3/51), was significantly higher. Corbett et al.[4,5] compared the radiographic findings of pulmonary tuberculosis and NTM pulmonary disease. Among patients with pulmonary tuberculosis, 37% (34/92) had radiographic findings consistent with pneumoconiosis, while among patients with *M. kansasii* and *M. scrofulaceum* pulmonary disease, 47% (43/92) and 69% (24/35), respectively, had such findings. Thus, the incidence of pneumoconiosis tended to be higher in NTM pulmonary disease compared with that in pulmonary tuberculosis. It is possible that pneumoconiosis, which, along with diabetes mellitus, a history of gastrectomy, and the use of corticosteroids, is a risk factor for pulmonary tuberculosis,[1,8] may also be related to NTM pulmonary disease. As far as we know, there are some reports on NTM pulmonary disease in patients with pneumoconiosis. However, there are few studies discussing the isolation of NTM from patients with pneumoconiosis.

In our study, NTM, including both pathogenic species and nonpathogenic species, were isolated from 39% of the patients with pneumoconiosis.[10] Common etiologic species, defined by the ATS in 1997,[7] were identified in 21 patients, unusual etiologic species were identified in 11 patients, and undefined species, which appeared to be nonpathogenic, were identified in 41 patients.

NTM pulmonary disease cannot be diagnosed solely on the basis of NTM isolation.[7,11] In order to make a diagnosis of NTM pulmonary disease, it is necessary to confirm whether deterioration in symptoms and in findings on radiographic examinations are evident in the patients from whom

Fig. 1A–F. Computed tomography (CT) scans. **A, B** Infiltrates are shown as new findings on CT scan in case 1. **C, D** A cavity is shown as a new finding on CT scan in case 2. **E, F** Progression of massive shadow is shown as a deterioration of CT findings on CT scan in case 6

the same species of NTM are repeatedly isolated. However, it was suggested by the ATS that it may be difficult to apply the clinical criteria to patients with pre-existing lung disease.[7] Thus, it seems to be difficult to confirm whether the clinical criteria for NTM pulmonary disease are satisfied in patients with pneumoconiosis, because nonspecific and persistent symptoms, such as cough, sputum, and dyspnea, can be caused by the pneumoconiosis itself. The same may be true of the radiographic criteria, as it seems to be difficult to evaluate radiographic findings such as infiltrates, cavities, multiple small nodules, and multifocal bronchiectasis, which can be observed in NTM pulmonary disease,[7] because various findings such as large opacities, small opacities, and pleural thickening can be observed in pneumoconiosis itself.[9] Therefore, detailed evaluation of the symptoms, radiographic findings, and backgrounds of patients who satisfy the bacteriologic criteria can be important in making a diagnosis of NTM pulmonary disease in patients with pneumoconiosis.

As a result of the identification of NTM species and the review of the frequency of their isolation in our patients with pneumoconiosis, eight patients satisfied the bacteriologic criteria for the diagnosis of NTM pulmonary disease. This group appeared to include patients with NTM pulmonary disease who could not be fully evaluated from the clinical or radiographic findings because of "pre-existing lung disease", although two of these patients did satisfy the ATS diagnostic criteria for NTM pulmonary disease. Therefore, the clinical course of these eight patients should be followed carefully.

The NTM species we isolated in conformity with the bacteriologic criteria from the above 8 patients were common etiologic species in 7 patients and nonpathogenic species in 1 patient. Thus, 7 of the 21 patients from whom common etiologic species were isolated satisfied the bacteriologic criteria, and 1 of the 41 patients from whom nonpathogenic species were isolated satisfied the bacteriologic criteria. Four of the 18 patients from whom *M. avium* were isolated satisfied the bacteriologic criteria, and 2 of these 4 patients satisfied the ATS diagnostic criteria for NTM pulmonary disease. All 3 patients from whom *M. intracellulare* were isolated, and the 1 patient from whom *M. kansasii* were isolated, also satisfied the bacteriologic criteria. Thus, the possibility of progression to NTM pulmonary disease may be considered in the patients from whom the common etiologic species were isolated although some isolation of *M. avium* may represent colonization. On the other hand, most of the patients from whom *M. gordonae* were isolated, and all patients from whom the other species were isolated, did not satisfy the bacteriologic criteria. Thus, the isolation of NTM that would not lead to NTM pulmonary disease was observed in patients with pneumoconiosis. These data were evaluated based on the criteria of the ATS,[7] because of international harmonization. However, it is necessary to note that some species, such as *M. gordonae*, *M. terrae*, *M. nonchromogenicum*, *M. chelonae*, and *M. scrofulaceum*, which were classified as neither common etiologic species nor unusual etiologic species, may be a cause of NTM pulmonary disease in Japan.[12]

Linear shadows or the progression of massive shadows, features which were observed in 3 of the 8 patients who satisfied the ATS bacteriologic criteria for NTM pulmonary disease, should be regularly followed with CT scans, in order to confirm whether they deteriorate to the findings observed in conformity with the radiographic criteria. We investigated the backgrounds of these 8 patients compared with the backgrounds of all the subjects (155 patients with pneumoconiosis) in this study. There were no distinctive differences in age, sex ratio, diabetes mellitus, history of gastrectomy, use of corticosteroids, history of occupational exposure to dust, or chest X-ray findings due to pneumoconiosis. Thus, it seems that these factors are not related to the progression to NTM pulmonary disease.

It is important to note that NTM, including both pathogenic species and nonpathogenic species, were isolated from patients with pneumoconiosis. Some of these patients satisfied the ATS bacteriologic criteria, and a few satisfied the ATS diagnostic criteria for NTM pulmonary disease.

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