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Clinical Analysis of Pulmonary Nontuberculous Mycobacterial Disease Diagnosed as Coincidental Pulmonary Infection Due to *Mycobacterium* Species*

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ABSTRACT

Objectives: We analyzed the clinical characteristics of patients with pulmonary mycobacterial disease diagnosed as coincidental pulmonary infection due to *Mycobacterium* species. **Materials and Methods:** One hundred sixty patients satisfied the diagnostic criteria of nontuberculous mycobacterial disease proposed by American Thoracic Society during the last seven years. Six patients (3.8%) were coincidental pulmonary infection due to two *Mycobacterium* species. We investigated the background, laboratory findings, microbiological findings, radiological findings, treatment and prognosis. **Results:** There were six patients, 3 males and 3 females, with a mean age of 71.7 years. The causative microorganisms of coincidental pulmonary infection consisted of *Mycobacterium avium* + *Mycobacterium intracellulare* in two patients, *Mycobacterium avium* + *Mycobacterium kansasii* in one, *Mycobacterium intracellulare* + *Mycobacterium chelonae* in one, *Mycobacterium intracellulare* + *Mycobacterium abscessus* in one, and *Mycobacterium intracellulare* + *Mycobacterium tuberculosis* in one. Regarding the radiological findings, the distribution of the lesion was frequently shown in both the right middle and left lingula lobes, but the extent of the lesion was limited within the unilateral lung field. Centrilobular small nodules with bronchiectasis were recognized in all patients and cavities or infiltration shadows were recognized in half of them on chest computed tomography. A definite diagnosis was obtained by bronchoalveolar lavage fluid in four patients and expectorated sputum in two. Combined chemotherapy was performed for two patients and that for pulmonary tuberculosis in one. **Conclusions:** Coincidental pulmonary infection due to *Mycobactterium* species occurred at a low percentage. Although most patients were elderly with underlying disease and clinical features were compatible with pulmonary *Mycobacterium avium* complex disease, the prognosis was comparatively good with and without treatment.

Keywords: Coincidental Pulmonary Infection; Mycobacterium Species

1. Introduction

Since the American Thoracic Society (ATS) proposed the diagnostic guidelines of pulmonary nontuberculous mycobacterial (NTM) disease in 2007 [1], the number of patients with pulmonary NTM disease has been increasing in Japan [2]. Of many causative microorganisms of pulmonary NTM disease, *Mycobacterium avium* is the most common pathogen, *Mycobacterium intracellulare* is the second, and *Mycobacterium kansasii* is the third one in Japan. Among the microbiological diagnostic criteria of pulmonary NTM disease, if positive culture results from at least two separate expectorated sputum samples or positive culture results from at least one bronchial wash or lavage are obtained, we can confirm a definite diagnosis of pulmonary NTM disease in combination with clinical findings.

Recently, because bronchoscopy has been frequently performed to obtain a definite diagnosis of pulmonary NTM disease and its diagnostic usefulness was reported [3,4], we sometimes discover coincidental pulmonary infection due to *Mycobacterium* species. There are few reports about the clinical characteristics of coincidental pulmonary infection due to *Mycobacterium* species as far as we investigated. Therefore, we clarified the clinical characteristics of patients with coincidental pulmonary infection due to *Mycobacterium* species during the last seven years in this study.

*The authors declare that they have no conflict of interest (COI).
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2. Materials and Methods

This study was approved by the institutional review board (Ethical Committee of Kawasaki Medical School). Informed consent from each patient was not required because all data were collected retrospectively. We selected one hundred and sixty patients who satisfied the diagnostic criteria of NTM disease proposed by ATS [5] in our hospital between January 2005 and December 2011. Among these patients, six patients (3.8%) had coincidental pulmonary infection due to two *Mycobacterium* species. We investigated the backgrounds, laboratory findings, microbiological findings, radiological findings, diagnostic methods, treatment and prognosis of these patients and the remaining patients with pulmonary NTM disease (154 patients) in this study.

All data from patients were drawn from charts, which included age, sex, smoking history and past medical history. Laboratory findings such as total protein or albumin showing nutritional condition purified protein derivatives (PPD) or QuantiFERON (QFT) and microbiological findings such as causative microorganisms or drug sensitivity tests using the Broth MIC method (Kyokuto Pharmaceutical Industrial Co. Ltd.), as well as the results of smear and culture tests for acid-fast bacilli, were reviewed. Radiological findings, such as portion, extension of lesion 1) within one-third of the unilateral lung field; 2) within the unilateral lung field; 3) over the unilateral lung field) for pulmonary NTM disease, bronchiectatic change, cavity, centrilobular small nodules, and infiltration shadows, were also reviewed. All radiological findings were evaluated on computed tomography (CT) scans of the chest by one pulmologist and one radiologist. In terms of treatment, the medication for pulmonary NTM disease was reviewed. Long-term follow-up was evaluated for these patients to investigate the prognosis.

3. Results

The clinical findings of the patients with coincidental pulmonary infection due to *Mycobacterium* species are shown in **Table 1**. Six patients (3.8%) had coincidental pulmonary infection due to two *Mycobacterium* species, including *Mycobacterium avium* complex (MAC). The mean age of the six patients was 71.7 years and there were three males and three females. Two patients had a smoking history. All patients had underlying diseases and one of six patients received immunosuppressive treatment.

Regarding the laboratory findings, nutritional conditions such as total protein or albumin were preserved except in one patient. PPD was positive for two patients tested and QFT was negative for all five patients tested. The causative microorganisms in patients with coincidental pulmonary infection due to *Mycobacterium* species consisted of *Mycobacterium avium* + *Mycobacterium intracellulare* in 2 patients, *Mycobacterium avium* + *Mycobacterium kansasii* in 1, *Mycobacterium intracellu-*

Table 1. Clinical findings of the patients with coincidental pulmonary infection due to *Mycobacterium* species.

Case	Age	Sex	Smoking history	Past history	Laboratory findings				Causative microorganisms	Drug-sensitivity test								
					TP (g/dl)	Alb (g/dl)	PPD	QFT (ZU/l)		SM	EB	KM	INH	RFP	LVFX	CAM	TM	AMK
1	61	M	(+)	Bronchial asthma Gastric ulcer Glaucoma	7.3	4.6	$\frac{0\times0}{10\times10}$	0.21	*M. avium* + *M. kansasii*	32 >128	4 16	64 >128	N.D. N.D.	8 2	1 >32	2 32	2 8	>16 >16
2	68	F	(−)	Breast Ca(ope)	6.7	4.1	N.D.	<0.05	*M. avium* + *M. intracellulare*	16 >128	>128 >128	64 128	>32 >32	4 8	8 8	1 2	>16 >16	16 >16
3	72	F	(−)	Gastric Ca(ope)	8	3.7	N.D.	<0.05	*M. intracellulare* + *M. chelonae*	16 16	>128 64	64 32	32 >32	0.5 8	4 2	1 0.125	16 8	8 >16
4	84	M	(−)	Gastric Ca(ope) Unstable angina	7.9	4.1	$\frac{0\times0}{20\times15}$	<0.05	M. intracellulare + M. abscessus	8 >128	>128 >128	64 32	32 >32	2 >32	4 16	0.5 32	>16 >16	8 >16
5	70	F	(−)	RA(Steroid) Basedow disease	6.4↓	3.4↓	N.D.	N.D.	*M. tuberculosis* + *M. intracellulare*	10 8	2.5 4	20 8	1 32	40 0.25	2	0.25	4	4
6	75	M	(+)	COPD	7	4	N.D.	<0.05	*M. avium* + *M. intracellulare*	32 4	>128 8	64 32	N.D. N.D.	4 0.125	32 1	4 0.5	>16 16	>16 4

TP: Total protein; Alb: Albumin; PPD: Purified protein delivatives; QFT: QuantiFERON; SM: Streptomycin; EB: Ethambutol; KM: Kanamycin; INH: Isoniazid; RFP: Rifampicin; LVFX: Levofloxacin; CAM: Clarithromycin; TH: Thionamide; AMK: Amikacin; RA: Rheumatoid arthritis; COPD: Chronic obstructive pulmonary disease.

lare + *Mycobacterium chelonae* in 1, *Mycobacterium intracellulare* + *Mycobacterium abscessus* in 1, and *Mycobacterium tuberculosis* + *Mycobacterium intracellulare* in 1, respectively. The results of drug sensitivity tests for several antibiotics are shown in **Table 1**. Although the minimum inhibitory concentration (MIC) showed higher concentrations of most antibiotics for *Mycobacterium kansasii* and *Mycobacterium abscessus*, it was preserved at lower concentrations of clarithromycin (CAM) for isolated MAC in most patients. The diagnostic methods used bronchoscopic specimens in four patients and expectorated sputum in two.

Concerning the radiological findings (**Table 2**), lesions due to pulmonary NTM disease existed within the unilateral lung field and bilaterally in all patients. All patients had centrilobular small nodules with bronchiectasis and three of six patients showed multiple cavitary lesions or infiltration shadows. These radiological findings resembled those of pulmonary MAC disease.

Anti-mycobacterium species treatment was prescribed for three patients after the diagnosis of pulmonary mycobacterial disease. The clinical effect was good for these three patients with an improvement in clinical symptoms and radiological findings. There were no complications with pulmonary NTM disease and the prognosis was comparatively good (all patients survived from one to seven years after a definite diagnosis).

The clinical findings of the patients with the remaining patients with pulmonary NTM disease (154 patients) are shown in **Table 3**. The mean age of these patients were younger and the frequency of patients with underlying disease was lower compared to those with coincidental pulmonary infection. The causative microorganisms in the remaining patients with pulmonary NTM disease consisted of *M. avium* in 73 patients, *M. intacellulare* in 60, *M. kansasii* in 14, and others in 7, respectively. Concerning the treatment, combined chemotherapy including antituberculous drugs was performed for half of these patients. The mortality rate was comparatively low and most of these patients died of other complications or underlying diseases.

4. Discussion

Since bronchoscopy has been frequently performed to obtain a definite diagnosis of pulmonary NTM disease, the number of patients with this disease has been increasing and the usefulness of bronchoscopy has been reported [3,4]. In this study, the frequency of coincidental infection due to *Mycobacterium* species was a low percentage (3.8%: 6/160) and two species including MAC were identified in all patients. In a previous report, Jarand *et al.* indicated that over half of patients with *Mycobacterium abscessus* pulmonary disease (55%) had coexistent, or a history of, pulmonary MAC disease [5]. They investigated the frequency of only coincident pulmonary infection due to both *Mycobacterium abscessus* and MAC and there are few epidemiological studies on coincidental pulmonary infection due to different several *Mycobacterium* species.

Regarding the background of patients with coincidental pulmonary infection due to *Mycobacterium* species,

Table 2. Clinical findings of the patients with coincidental pulmonary infection due to *Mycobacterium* species.

Case	Radiological findings						Diagnostic methods	Treatment	Clinical effect	Complication	Prognosis
	Portion	Extent of lesion※	Cavity	Bronchiectatic change	Centriliobular small nodules	Infiltration shadow					
1	Bilateral	2	(+)	(+)	(+)	(+)	BALF (Smear(+), Culture(+))	RFP + EB + CAM + S (6 months)	Good	(−)	Survival (1 year)
2	Bilateral	1	(−)	(+)	(+)	(−)	BALF (Smear(−), Culture(+))	(−)		(−)	Survival (7 years)
3	Bilateral	2	(+)	(+)	(+)	(+)	Sputum (Smear(+), Culture(+)	CAM + EB + SM + LVFX (1 year)	Good	(−)	Survival (3 years)
4	Bilateral	2	(+)	(+)	(+)	(+)	BALF (Smear(+), Culture(+))	(−)		(−)	Survival (3 years)
5	Bilateral	2	(−)	(+)	(+)	(−)	Sputum (Smear(+), Culture(+))	INH + RFP + EB + PZA (6 months)	Good	(−)	Survival (2 years)
6	Bilateral	2	(−)	(+)	(+)	(−)	BALF (Smear(+), Culture(+))	(−)		(−)	Survival (1 year)

BALF: Bronchoalveolar lavage fluid; ※1: Within one-third of the unilateral lung field; 2: Within the unilateral lung field; 3: Over the unilateral lung field.

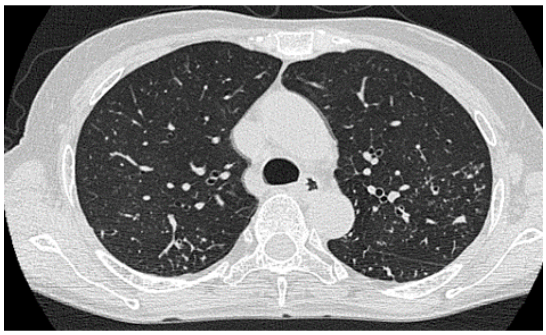
Table 3. Clinical findings of the patients with pulmonary NTM disease excluding the patients with coincidental pulmonary infection due to *Mycobacterium* species (154 cases).

Age (Mean ± S.D., years)		68.5 ± 10.4
Sex (Male:Female)		61:93
Smoking history (+)		70 (45%)
Underlying disease (+)		108 (70%)
	Respiratory disease	46 (30%)
	Non-respiratory disease	62 (40%)
Causativemicroorganisms		
M. avium		73 (47%)
M. intracellulare		60 (39%)
M. kansasii		14 (9%)
Others		7 (5%)
Radiological findings		
Portion	Bilateral	109 (71%)
	Unilateral	45 (29%)
Extension #	1	60 (39%)
	2	78 (51%)
	3	16 (10%)
Cavity		95 (62%)
Bronchiectatic change		137 (89%)
Diagnostic methods		
Sputum		72 (47%)
BALF		71 (46%)
Others		11 (4%)
Treatment		
Combined chemotherapy		80 (52%)
Surgical operation		6 (4%)
Prognosis		
Died		18 (12%)

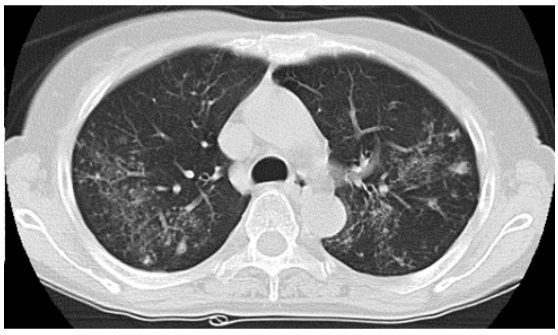
BALF: Bronchoalvelar lavage fluid;
1 : Within one-third of unilateral lung field
2 : Within unilateral lung field
3 : Over unilateral lung field

elderly patients with underlying diseases such as respiratory diseases or malignancies were common, as in previous reports [6,7], but nutritional conditions were preserved except in one case.

The radiological findings of 6 patients with pulmonary MAC disease such as centrilubular small nodules with bronchiectatic changes mainly in the right middle lobe or left lingula segment were a common characteristic. Radiological abnormalities of pulmonary MAC disease have been classified into the following five patterns on the basis of chest CT: nodular and bronchiectatic disease, fibrocavitary disease, solitary nodule disease, hypersensitivity disease, and disseminated disease [1]. Of the five patterns, nodular and bronchiectatic disease was the most frequent and fibrocavitary disease was the second most frequent in previous reports. All patients had MAC as causative microorganisms of coincidental pulmonary infection in this study. The radiological findings of *Mycobacterium abscessus* or *Mycobacterium chelonae* pulmonary disease have been said to resemble those of MAC pulmonary disease in previous reports [1,5,8]. On the other hand, the radiological findings of *Mycobacterium kansasii* pulmonary disease or pulmonary tuberculosis had characteristic thin or thick cavities located in the apical segment [9]. We think that it is difficult to suggest the causative microorganism from the radiological findings in patients with coincidental pulmonary infection due to *Mycobacterium* species based on this study. We followed-up patients with pulmonary MAC disease, and *Mycobacterium tuberculosis* were also isolated simultaneously from one patient (Case 5). She was receiving immunosuppressive treatment (corticosteroid drugs) and was in a poor nutritional condition. Because new lesion appeared in the bilateral upper lobe on periodical chest CT (**Figure 1**), the attending physician performed an acid-fast bacilli examination and, finally, *Mycobacterium tuberculosis* was detected. Physicians must be careful when treating immunocompromised patients complicated with pulmonary tuberculosis.



(a)



(b)

Figure 1. (Case 5) Coincidental pulmonary infection due to *Mycobacterium intracellulare* and *Mycobacterium tuberculosis*. New lesion with centrilobular small nodules on chest CT appeared in the bilateral upper lobe. (a) 2009.10; (b) 2010.11.

Concerning the diagnostic methods, the bronchoscopic procedure is important to acquire accurate information about coincidental pulmonary infection due to *Mycobacterium* species. In this study, four of six patients were given an accurate diagnosis using bronchoalveolar lavage fluid (BALF). Although bronchoscopy is an invasive technique, we think it is necessary to consider a differential diagnosis of pulmonary NTM disease.

Regarding the selection of treatment, ATS/IDSA proposed a guideline for treatment of pulmonary NTM disease in 2007 [1]. The therapy for pulmonary MAC disease was recommended as combined chemotherapy including a macrolide (clarithromycin (CAM) or azithromycin (AZM)), ethambutol (EB), rifampicin (RFP) ± aminoglycoside depending on disease status and/or severity. On the other hand, therapy for pulmonary *Mycobacterium abscessus* or *Mycobacterium chelonae* disease was recommended as combined chemotherapy consisting of a macrolide, aminoglycoside, imipenem and cefoxitin and that for pulmonary *Mycobacterium kansasii* disease was combined chemotherapy including isoniazid (INH), RFP and EB. There is a little difference in the treatment between *Mycobacterium* species. Therefore, it is important to identify the species in NTM. However, the clinical effect of combined chemotherapy for pulmonary NTM disease except for pulmonary *Mycobacterium kansasii* disease was not good (clinical symptoms and/or abnormal radiological findings) [10]. There are no guidelines for initiating or ending treatment or the adaptation of treatment for elderly patients. Consequently, combined chemotherapy was performed for three of six patients because there were mainly elderly patients in this study; multi-drug chemotherapy including CAM for two patients and antituberculous treatment for *Mycobacterium tuberculosis* for one. The clinical effect due to combined chemotherapy was good and the prognosis was also good despite their general condition. We do not think there was a relationship between coincidental pulmonary infection and clinical effect or prognosis of the subjects in this study.

There are a few limitations in this study. Firstly, there were only a few patients with coincidental pulmonary infection due to *Mycobacterium* species among patients with pulmonary mycobacterial disease in one hospital in a restricted area, so we need to perform a large-scale study including several hospitals in Japan to get an accurate of coincidental mycobacterial infection. Secondly, the rate of coincidental mycobacterial infection was lower than in other reports [5]. This is because the diagnostic accuracy of the acid-fast bacilli culture was poor in our laboratory when patients with coincidental infection due to *Mycobacterium* species were tested.

In conclusion, the rate of coincidental pulmonary infection due to *Mycobacterium* species was a low percentage and clinical characteristics were similar to those of pulmonary MAC disease mainly on the radiological findings. Although most patients were elderly with underlying diseases, the clinical effect and prognosis were comparatively good.

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