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【 ORIGINAL ARTICLE 】

Clinical Features of Nontuberculous Mycobacterial Pleurisy: A Review of 12 Cases

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Abstract:

Objective The incidence of pulmonary nontuberculous mycobacterial (NTM) infections has increased in recent decades. Nevertheless, NTM pleurisy is still a rare disease. The objective of the present study was to elucidate the clinical features and outcomes of NTM pleurisy.

Methods A retrospective study was undertaken of consecutive patients whose pleural effusion culture yielded NTM, from 2002 to 2016 at a respiratory hospital in Japan. The clinical features, treatment, and outcomes of these patients were analyzed.

Result The 12 patients with NTM pleurisy were predominantly male, with a median age of 69 years (range, 48-93 years). They included eight patients with a history of smoking and six patients with immunosuppressive comorbidities such as malignancy, diabetes mellitus, and conditions requiring steroid administration. Fibrocavitary disease was the most common radiographic feature of these patients, and *Mycobacterium avium* complex was the most common pathogen. Pneumothorax was complicated in 11 patients. Surgery was performed on seven patients, in addition to thoracic drainage for the treatment of pleurisy and pneumothorax. Three patients died of respiratory failure.

Conclusion Pneumothorax is a frequent complication of NTM pleurisy, often making the condition difficult to treat. Surgery at an appropriate time should therefore considered for refractory cases.

Key words: nontuberculous mycobacterium, pleurisy, pneumothorax

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Introduction

Pulmonary nontuberculous mycobacterial (NTM) infections have been increasing worldwide in the past few decades (1-3). Although the precise reasons for this phenomenon have not yet been clearly elucidated, possible contributory factors include the increase of aging populations and various immunocompromised conditions, as well as an enhanced recognition of NTM and improvements in bacterial detection techniques (4). NTM-related mortality is also reported to be increasing (5). Although pulmonary NTM infection is often chronic, some patients may experience rapidly progressive disease (6).

NTM pleurisy is suspected to have a high mortality rate, but it is rarely seen compared to pleurisy caused by *Mycobacterium tuberculosis* (7). Because of its rarity, the clinical features of NTM pleurisy remain unknown. We therefore conducted a retrospective study, to elucidate the clinical features and outcomes of NTM pleurisy.

Materials and Methods

Study subjects

We reviewed the mycobacterial laboratory registry data-

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Table 1. Patient Characteristics (n=12).

Age, years, median (range)	69 (48-93)	
Sex		
Male	9	
Female	3	
Smoking history		
Yes	8	
No	4	
Immunosuppressed factor		
Malignancy	1	
Diabetes mellitus	4	
Steroid administration	3	
Body mass index, kg/m^2, median (range)	21.2 (15.4-22.5)	
Laboratory (serum)	median	(range)
WBC, /μL	7,500	(2,100-14,200)
Hb, g/dL	11.8	(8.5-14.5)
TP, g/dL	7.1	(5.2-7.9)
Alb, g/dL	3.2	(2.1-4.2)
CRP, mg/dL	7.1	(2.2-26.9)
Appearance of pleural effusion		
Yellow	4	
Bloody	1	
Purulent	1	
Unknown	6	
Predominant cell of pleural effusion		
Lymphocyte	5	
Neutrophil	2	
Unknown	5	
Laboratory (pleural effusion)	median	(range)
pH	7.2	(7.0-7.4)
LDH, U/L	760	(256-8,970)
Glucose, mg/dL	93	(1-238)
Total protein, g/dL	4.2	(3.3-5.2)
ADA, U/L	59.8	(29.8-73.2)

Table 2. Radiologic Findings (n=12).

Disease type		
	NB	3
	FC	5
	Unknown	4
Cavity		
	Right	6
	Left	0
	Bilateral	2
	Unknown	4
Pneumothorax		
	Right	8
	Left	3
	None	1

NB: nodular/ bronchiectatic disease, FC: fibrocavitary disease

base and examined consecutive pleural effusion (PE) samples sent for mycobacterial culture from January 1, 2002 to June 30, 2016 at the Kinki-Chuo Chest Medical Center, a 450-bed respiratory disease hospital in Osaka, Japan. Patients with at least one cultured PE sample positive for NTM were identified. Among these patients, those with accompanying clinical symptoms (fever, chest pain) and/or elevated serum inflammatory markers (C-reactive protein or white blood cell count) were defined as NTM pleurisy patients.

The clinical characteristics, treatment course, and outcomes of NTM pleurisy patients were analyzed. Pulmonary NTM infection was defined according to American Thoracic Society/ Infectious Diseases Society of America guidelines (6).

This study was approved by the institutional review board of our hospital. (Approval number: 555) Since all data were collected retrospectively, obtaining informed consent from each patient was not required.

Radiographic assessment

Computed tomography (CT) findings were evaluated by three trained pulmonologists. The two major radiological findings diagnostic of pulmonary NTM infection were fibrocavitary (FC) disease and nodular/bronchiectatic (NB) disease (6). Upper lung field fibrocavitary lesions, a tuberculosis like pattern, were defined as FC disease, while multiple nodules and bronchiectasis, typically seen in the middle lobe or lingula, were defined as NB disease (8). The type of pulmonary NTM infection, and the presence of cavitary lesions and pneumothorax were also analyzed.

Results

During the study period, 4097 PE samples were sent for mycobacterial culture. Among these samples, 14 PE samples yielded NTM. Since the medical records of two of these patients were not available, they were excluded from the study, and the clinical manifestations of 12 patients were analyzed. All of these 12 patients were accompanied by clinical symptoms and elevated serum inflammatory markers.

The patient characteristics are shown in Table 1. The median age was 69 years, and they included nine men and three women. Of these, eight patients had a history of smoking, and six patients had immunosuppressive comorbidities such as malignancy, diabetes mellitus, and conditions requiring steroid administration. The median body mass index was 21.2 kg/m^2, and the median serum albumin level was 3.2 g/dL. One patient had a purulent PE suggesting empyema. The median adenosine deaminase level of PE was 59.8 U/L. Lymphocyte predominated in five samples and neutrophils in two samples.

Radiological findings

The findings from CT images are shown in Table 2. The most common NTM disease type seen was FC disease (five patients); NB disease was seen in four patients. Emphyse-

Table 3. Patients with Nontuberculosis Pleurisy (n=12).

Case	Age, sex	Mycobacterium species(PE)	Medical history	Medication before onset	Medication after onset	Time until onset of plerisy from diagnosis of NTM	Pneumothorax	Treatment other than medication	Outcome
1	59, M	*M.kansasii*	RA	INH, RFP, EB, PZA	INH, RFP, EB, PZA	same time	(+)	drainage+surgery	improved
2	69, M	*M.avium*	SCLC, Radiation pneumonitis	none	none	unknown	(-)	none	death
3	72, M	*M.intracellulare*	Urinary calculus	RFP, EB, CAM	RFP, EB, CAM	4 years 7 months	(+)	drainage+surgery	improved
4	93, F	*M.avium*	Osteoporosis	RFP, EB, CAM	RFP, EB, CAM	1 year 8 months	(+)	drainage	improved
5	60, M	*M.avium*	DM, Tb	none	RFP, EB, CAM	same time	(+)	drainage+surgery	improved
6	77, M	*M.chelonae*	ICH, HT, Liver cirrhosis	none	none	unkown	(+)	none	no change
7	48, M	*M.kansasii*	Pneumothorax	RFP, EB, CAM	RFP, EB, CAM	1month	(+)	drainage+surgery	improved
8	69, F	*M.intracellulare*	none	RFP, CAM, STFX	RFP, CAM, AMK	18 years 10 months	(+)	drainage	death
9	71, M	*M.avium*	DM, OMI, Asthma	RFP, EB, CAM	RFP, EB, CAM	4 years 9 months	(+)	drainage+surgery	death
10	84, M	*M.abscessus*	DM, OMI	RFP, EB	RFP, EB, CAM	4 months	(+)	drainage	improved
11	61, F	*M.avium*	HT, Aspergillosis	RFP, EB, CAM	RFP, EB, CAM, SM	4 years 2 months	(+)	drainage+surgery	improved
12	66, M	*M.intracellulare*	DM, Chronic hepatitis C, COPD, IPF	none	RFP, EB, CAM	3 years 9 months	(+)	drainage+surgery	improved

RA: Rheumatoid arthritis, SCLC: Small cell lung cancer, DM: Diabetes mellitus, Tb: Pulmonary tuberculosis, ICH: Intracerebral hemorrhage, HT: Hypertension, OMI: Old myocardial infarction, COPD: Chronic obstructive pulmonary disease, IPF: Idiopathic pulmonary fibrosis, INH: Isoniazid, RFP: Rifampicin, EB: Ethambutal, PZA: Pyrazinamide, CAM: clarithromycin, STFX: Sitafloxacin, AMK: Amikacin, SM: Streptomycin

matous lesions were seen in four patients, all of whom were smokers. Cavitary lesions due to pulmonary NTM were seen in eight patients. Pneumothorax was seen in 11 out of 12 patients, and pleurisy always occurred on the same side as pneumothorax.

NTM species and courses of treatment

The NTM species yielded from the PE were *Mycobacterium avium* in five patients, *M. intracellulare* in three, *M. kansasii* in two, *M. abscessus* in one, and *M. chelonae* in one (Table 3). Before the onset of NTM pleurisy, eight patients had received anti-NTM medication, and the time from the diagnosis of pulmonary NTM disease until the onset of pleurisy varied widely from simultaneously to more than 18 years. As described above, pneumothorax was a complication in 11 patients. Only two patients were cured via anti-NTM medication and thoracic drainage alone. Surgery was performed on seven patients, three of whom required multiple operations. Open-window thoracotomy was performed on three patients, debridement on two, and thoracotomy for pneumothorax on four. Granulomatous inflammation was seen in the resected tissue of three patients.

In spite of performing multidisciplinary treatment, three out of 12 patients died. One of these three patients had been suffering from small cell lung cancer when NTM pleurisy occurred. Since the patient's general condition was poor, surgery was not indicated; the coexistence of pneumothorax, NTM pleurisy and lung cancer let to fatal respiratory failure in that case. The other two patients who died were on medication for chronic refractory pulmonary NTM infection; the response to the medication was poor, and they developed NTM pleurisy. Surgery was performed on one patient, but it was not indicated for the other. Eventually, both died of progressive respiratory failure.

Discussion

Although pleurisy is an uncommon complication of pulmonary NTM disease (9-12), it has become a clinical concern because of the increasing prevalence of NTM disease. During the 13-year study period at our hospital, NTM was isolated from PEs in 14 patients.

In our study, NTM pleurisy was more common in men than in women. Furthermore, FC disease was seen slightly more frequently than NB disease. FC disease is more common in older male smokers, while NB disease more frequently occurs in middle-aged or older women with no smoking history (1). The prevalence of NB disease in Japanese women has increased in the past few decades, and it is now the most common type of pulmonary NTM disease (13, 14). However, in the present study, male patients with FC disease were more frequently seen. A male sex, the presence of systemic and/or respiratory comorbidities, and non-NB radiographical features are reported to be negative prognostic factors for pulmonary *M. avium* complex disease (8). These factors may overlap with the characteristics

often seen in NTM pleurisy patients.

How the NTM infection reaches pleural effusion has not yet been adequately explained; however, there are two hypotheses regarding the pathway: The first hypothesized mechanism is the infiltration of the infectious pulmonary lesion; the second is the leakage of NTM bacteria from the pulmonary lesion to the thorax through perforating foci, such as those present in pneumothorax (15). In our research, 11 out of 12 patients had pneumothorax. In spite of NTM pleurisy without pneumothorax being reported (7), pneumothorax may be one of the causes of NTM pleurisy. Since cavitary lesions were often seen in our research, pulmonary NTM disease itself may sometimes cause pneumothorax, as well as underlying respiratory disease. In fact, pneumothorax due to the perforation of cavity lesions caused by NTM infection has been reported, which was also demonstrated in specimens resected by surgery (16).

Anti-NTM chemotherapy is generally associated with better outcomes for the treatment of NTM pleurisy (6). Nevertheless, cases of NTM infection that are difficult to treat medically are often seen in clinical practice and are also reported (5, 6). Since most of the patients were complicated with pneumothorax, surgery was necessary in addition to medication and thoracic drainage. According to our research, NTM pleurisy with pneumothorax tends to have a poor prognosis. For those with a poor general condition and infection due to mycobacterial species resistant to chemotherapy, NTM pleurisy and pneumothorax may be fatal. Even those with mild underlying disease may require several operations to achieve successful treatment. Therefore, timely surgery might be needed to cure NTM pleurisy with pneumothorax before the patient's condition worsens.

There are several limitations associated with this study. First, as this was a retrospective study, some clinical and laboratory records were not available. Moreover, the number of patients with NTM pleurisy may have been underestimated, since mild pleural effusion was not routinely investigated and a mycobacterial culture was not performed on every PE sample. Lastly, we studied only a small number of patients at a single institution; in order to obtain more information about NTM pleurisy, large-scale studies are needed.

Conclusion

NTM pleurisy may occur in men with a history of smoking and the radiological features of FC disease. The treatment of NTM pleurisy is especially difficult when pneumothorax is complicated. If thoracic drainage and medication are ineffective, then surgery should be considered without delay.

The authors state that they have no Conflict of Interest (COI).

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