Clinical Features and Prognosis of Nontuberculous Mycobacterial Pleuritis

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Keywords

Nontuberculous mycobacteriosis · Pleuritis · Pneumothorax · Bronchopleural fistula · Drainage

Abstract

Background: While nontuberculous mycobacterial (NTM) pleuritis rarely complicates pulmonary NTM infection, high mortality has been reported in case reports and small studies. **Objectives:** The purpose of this study was to clarify the clinical features and treatment outcomes of pulmonary NTM infection cases accompanied by NTM pleuritis. **Methods:** Medical records of 1,044 patients with pulmonary NTM disease were retrospectively reviewed to select patients complicated by NTM-proven pleuritis. We investigated clinical characteristics, pathogens, pleural effusion examinations, radiographic findings, treatments, and clinical course of the NTM pleuritis patients. **Results:** Among 1,044 cases with pulmonary NTM, NTM pleuritis occurred in 15 cases (1.4%). The mean age was 69 years with a performance status of mostly 2 or better (80.0%), and 6 cases (40.0%) were complicated by pneumothorax. Subpleural cavities were radiologically detected in 11 cases (73.3%), and extrapulmonary air-fluid level was detected in 14 cases (93.3%). Eleven patients were

treated with combinations of 2–4 antimycobacterial drugs, including clarithromycin, and 2 patients were treated with isoniazid, rifampicin, and ethambutol. Chest tube drainage was performed in 11 cases, and surgical approach was added in 6 cases. The pleural effusion of 2 patients treated with only antimycobacterial medications gradually deteriorated. Two patients died from NTM pleuritis, and 1 patient died from pneumonitis during a mean of 1.8 years of follow-up. **Conclusions:** Comorbid NTM pleuritis was difficult to treat by medical therapy alone and resulted in a poor prognosis. In addition to antimycobacterial agents, chest tube drainage and surgical procedures in the early stages should be considered to treat NTM pleuritis.

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Introduction

Nontuberculous mycobacterium (NTM) is ubiquitous in the environment, frequently isolated from water and soil [1, 2]. Thus, most NTM organisms detected from human samples have been considered as colonization or contamination. However, NTM can cause diseases, such as lung infections, lymphadenopathy, skin and soft tissue

infections, and disseminated disease, in immunocompromised patients [3–5]. Since the guidelines on pulmonary NTM were pronounced by the American Thoracic Society (ATS)/Infectious Diseases Society of America (IDSA) [6], the prevalence of NTM infection has been reported worldwide [7–11]. The estimated incidence rate in Japan has increased from 1.5 per 100,000 in 1985 to 14.7 per 100,000 in 2014 [12]. The 3 most common pulmonary pathogen groups are *Mycobacterium avium* complex (MAC), *M. kansasii*, and *M. abscessus* complex in Japan [13].

While bronchopulmonary infection is one of the most common pathologies with NTM, NTM infection of the pleural space is rare in contrast to tuberculosis. Some studies reported cases of disseminated *M. avium* complex complicated by NTM pleuritis in immunocompromised patients [14, 15], and other cases of NTM pleuritis were reported in immunocompetent cases [16–22]. In the previous studies, the frequency of pleural effusion in patients with NTM infection was reported to be 3.4–6% [23, 24], although those reports did not state whether mycobacterial organisms were isolated from the pleural effusion.

Only a few studies in the literature have reported on the pathogenesis, clinical course, or prognosis of NTM pleuritis, concluding that the mortality was as high as 37–66% at 1 year [25, 26]. The aim of this study was to clarify the clinical characteristics and prognosis of NTM pleuritis complicating pulmonary NTM disease.

Materials and Methods

Patient Population

We retrospectively reviewed the medical records of 1,044 patients at our institution with pulmonary NTM disease meeting the 2007 ATS/IDSA criteria between January 2007 and December 2016 [6]. The study population with NTM pleuritis was selected with the additional criteria (1) positive culture of NTM from pleural effusion or pleural biopsy or (2) positive smear of pleural effusion or pleural biopsy and positive result of nucleic acid amplification test for *M. avium* complex. All laboratory data and images in this report were obtained as part of routine tests in the process of diagnosis and treatment.

Laboratory Test of Pleural Effusion

The aspirated pleural effusion sample was divided into 3 parts which were used for laboratory testing and microbiological and histological studies. Microbiological studies included acid-fast bacillus smear by Ziehl-Neelsen staining or fluorescent staining method and culture using the BACTEC MGIT 960 system (MGIT) or the Ogawa media, with the remaining sample being processed for transcription-reverse transcription concerted reaction [27].

Imaging Studies and Evaluation of Chest Computed Tomography Findings

We performed chest radiography and computed tomography in all patients on admission to evaluate NTM pleuritis. The imaging studies were reviewed by 1 general diagnostic radiologist and at least 2 pulmonologists who had 5–30 years of experience in thoracic imaging to evaluate the following points: the affected area, the pattern of abnormalities (i.e., nodular bronchiectasis or fibrocavitary pattern), presence or absence of subpleural cavities, extrapulmonary air-fluid level, pneumothorax, and pleural effusion. We evaluated the amount of pleural effusion with chest radiography or computed tomography taken at the onset of the disease. The amount of pleural effusion was estimated as small (less than one-third of 1 hemithorax with chest radiography), moderate (between one-third and two-thirds of 1 hemithorax), or large (more than two-thirds of 1 hemithorax) [28].

Evaluation of Clinical Features and Prognosis

We retrospectively investigated clinical characteristics, pathogens, pleural effusion examinations, radiographic findings, treatments, clinical course, and prognoses of the 15 cases with NTM-proven pleuritis. We used the Zubrod performance status to estimate patients' functional capacities [29]. Patients were followed up for at least 2 years after diagnosis or until death or loss to follow-up.

Statement of Ethics

This study was approved by the Institutional Review Board of National Hospital Organization Tokyo National Hospital (approval date: July 22, 2013; approval number: 140036). Because of the retrospective nature of the study, informed consent was not obtained from study participants. Waiver of consent to use the patient records was granted by the Institutional Review Board, and analysis of this study was carried out after anonymization of the patients' data.

Results

Characteristics of NTM Pleuritis

Between January 2007 and December 2016, in 1,044 cases with pulmonary NTM, pleuritis with NTM occurred in 15 cases (1.4%). Their mean age was 69 years, ranging from 46 to 85 years, and 9 patients (60%) were male (Table 1). While body mass index was lower than 18.5 in 11 cases (73%), performance status was 2 or better in 12 cases (80%). NTM pleuritis occurred with pneumothorax in 6 cases (40%). Two patients had diabetes mellitus, while the other patients were immunocompetent.

Pathogens isolated from the pleural effusion were identified as *M. avium* in 60% (9/15), followed by *M. kansasii* in 13% (2/15) (Table 2). NTM and bacteria were isolated at the same time in 2 cases (13%), and these patients were diagnosed as coinfection with other bacteria. Differential cell counts in pleural effusion were available in 12 cases, exhibiting neutrophil predominance in 9 cases

Table 1. Clinical characteristics of patients with NTM pleuritis (*n* = 15)

Age, years	69.2±10.6
Male gender	9 (60)
BMI ≤18.5	11 (73)
Performance status ≥2	12 (80)
Smoking history	9 (60)
Respiratory failure	3 (20)
Complications	
Pneumothorax	6 (40)
Diabetes mellitus	3 (20)
Past history of tuberculosis	5 (33)
Laboratory data	
WBC count, µL	8,260±1,425
Albumin, g/dL	3.0±0.7
CRP, mg/dL	8.9±5.8

Figures are means ± standard deviations or *n* (%). NTM, nontuberculous mycobacterium; BMI, body mass index; WBC, white blood cell; CRP, C-reactive protein.

(75%), including 2 cases of coexisting bacterial empyema. Adenosine deaminase (ADA) activity in the pleural effusion was available in 10 patients, and the mean ADA level was 152.7 U/L, ranging from 43.4 to 303 U/L.

Radiological Findings

Chest X-ray revealed that the area of the affected lung exceeded 50% of the total lung field in 11 cases (73%) (Table 3). Chest computed tomography predominantly showed nodular bronchiectasis in 5 patients and fibrocavitary features in 10 patients. Subpleural cavities were detected in 11 cases (73%). Air-fluid level was detected in the pleural spaces in 14 cases (93%), which made us suspect the presence of bronchopleural fistula. Pleural effusion was detected unilaterally in all cases (8 cases on the right). The amount of pleural effusion at the onset of NTM pleuritis was small in 14 patients (93%) and moderate in 1 patient (7%).

Clinical Course of NTM Pleuritis

In 7 of 15 cases (47%), NTM pleuritis developed within 2 years after the diagnosis of pulmonary NTM, whereas in 4 patients (27%) pulmonary NTM was diagnosed simultaneously with pleuritis (Table 4). Preexisting pulmonary NTM had not been treated with chemotherapy in 6 of 11 cases. After the diagnosis of NTM pleuritis, 11 patients were treated with 2–4 antimycobacterial medications (Table 4). Two cases with coexisting bacterial em-

Table 2. Clinical findings of pleural effusion

Pathogens (<i>n</i> = 15)	
<i>Mycobacterium avium</i>	9 (60)
<i>Mycobacterium kansasii</i>	2 (13)
<i>Mycobacterium intracellulare</i>	1 (7)
<i>Mycobacterium abscessus</i> complex	1 (7)
<i>Mycobacterium fortuitum</i>	1 (7)
<i>Mycobacterium scrofulaceum</i>	1 (7)
Differential cell counts (<i>n</i> = 12)	
Neutrophil predominant	9/12 (75) ^a
Lymphocyte predominant	3/12 (25)
ADA, U/L (<i>n</i> = 10)	
Mean ± SD	152.7±86.7
Range	43.4–303

Figures in parentheses are percentages. ADA, adenosine deaminase; SD, standard deviation. ^a Bacterial empyema coexisted in 2 cases.

Table 3. Radiological findings of NTM pleuritis (*n* = 15)

Lung lesion over 50% of the total lung field	11 (73)
Nodular bronchiectasis dominant	5 (33)
Fibrocavitary features dominant	10 (67)
Subpleural cavities present	11 (73)
Air-fluid level present in the pleural space	14 (93)
Pleural thickening	11 (73)
Amount of pleural effusion ^a	
Small	14 (93)
Moderate	1 (7)
Large	0 (0)

Figures in parentheses are percentages. NTM, nontuberculous mycobacterium. ^a Small = less than one-third of 1 hemithorax with chest radiography; moderate = between one-third and two-thirds of 1 hemithorax; large = more than two-thirds of 1 hemithorax.

pyema were treated only with antimicrobial agents not effective against NTM. Chest tube drainage was performed in 11 cases, and in 6 of the 11 cases surgical approaches were added (Table 4). While pleural biopsies were performed in all 6 cases, acid-fast bacillus smears were positive in 3 patients and cultures of pleural tissue were positive in 2 patients (Fig. 1). Three patients, including 2 cases with coexisting bacterial empyema, were lost to follow-up. The amount of pleural effusion of 2 alive

Table 4. Clinical course of the 15 patients

Age (years), sex	Period from pulmonary NTM to pleuritis	Pathogens	Chemotherapy before pleuritis	Pneumo-thorax	Chemotherapy after pleuritis	Drainage	Additional surgical procedure ^a	Clinical course
46, male	6 years	<i>M. avium</i>	(–)	(–)	CAM, RFP, EB, KM	(+)	(+)	alive (9 years)
69, male	1 year	<i>M. fortuitum</i>	(–)	(–)	CAM, LVFX, AMK	(+)	(+)	alive (9 years)
70, male	simultaneous	<i>M. abscessus</i>	(–)	(–)	CAM, IMP/CS, AMK	(+)	(+)	alive (7 years)
74, female	4 years	<i>M. avium</i>	CAM, GRNX (6 months)	(+)	CAM, EB	(+)	(+)	alive (2 years)
64, male	10 months	<i>M. avium</i>	(–)	(+)	CAM, RFP, EB, KM	(+)	(+)	alive (5 years)
57, male	simultaneous	<i>M. kansasii</i>	(–)	(+)	INH, RFP, EB	(+)	(–)	lost to follow-up
78, male	5 years	<i>M. intracellulare</i>	CAM, RFP, EB (4 years)	(–)	CAM, RFP, EB, KM	(–)	(–)	dead (3 months) by NTM pleuritis
75, male	simultaneous	<i>M. avium</i>	(–)	(–)	antibiotics	(+)	(–)	lost to follow-up
57, female	simultaneous	<i>M. avium</i>	(–)	(+)	CAM, EB, LVFX, KM	(+)	(+)	alive (3.5 years)
78, male	3 months	<i>M. avium</i>	CAM, RFP, EB (3 months)	(–)	CAM, RFP, EB, KM	(–)	(–)	alive (3.5 years)
73, female	1 year	<i>M. kansasii</i>	(–)	(–)	INH, RFP, EB	(–)	(–)	alive (4.5 years)
81, female	5 years	<i>M. avium</i>	CAM, RFP, EB (3 years)	(+)	CAM, RFP, EB, KM	(+)	(–)	alive (5 years)
75, female	10 years	<i>M. scrofulaceum</i>	(–)	(+)	CAM, RFP, EB, KM	(+)	(–)	dead (1 month) by NTM pleuritis
85, female	40 years	<i>M. avium</i>	(–)	(–)	antibiotics	(–)	(–)	lost to follow-up
56, male	8 years	<i>M. avium</i>	CAM, RFP, EB (7 years)	(–)	CAM, RFP, EB, KM	(+)	(+)	dead (5 years) by pneumonia

NTM, nontuberculous mycobacterium; CAM, clarithromycin; RFP, rifampicin; EB, ethambutol; KM, kanamycin; LVFX, levofloxacin; AMK, amikacin; GRNX, garenoxacin; IMP/CS, imipenem/cilastatin; INH, isoniazid. ^a Fenestration operation, pyothorax curettage, and thoracoplasty.

patients treated only with antimycobacterial medications in consideration of age, performance status, and general condition gradually deteriorated. Two patients died from NTM pleuritis, and 1 patient died from pneumonitis during a mean of 1.8 years of follow-up. The median survival period of the 3 dead patients from the diagnosis of NTM pleuritis was 3 months.

Discussion

NTM pleuritis is an uncommon condition that has been reported in immunocompromised hosts [14, 15]. As the prevalence of NTM infection has been increasingly reported worldwide, the number of case reports on NTM pleuritis has increased. Kobashi et al. [26] revealed that pneumothorax occurred in 4.1% of NTM patients and

NTM pleuritis arose secondarily in one-third of the pneumothorax cases. Ichiki et al. [23] reported that the frequency of pleural effusion in patients with pulmonary NTM was 3.4%. In our report, 1.4% of cases with pulmonary NTM developed pleuritis with NTM isolated from pleural effusion. The most common pathogen of the pleuritis was *M. avium*, followed by *M. kansasii* and *M. intracellulare*, similar to previous reports [25]. There were 2 cases of NTM pleuritis coexisting with another bacterial infection. Although these cases fulfilled our criteria of NTM pleuritis, NTM in the pleural effusion may not have pathogenic significance because these patients improved with only antibacterial therapy. Most of our cases revealed a high leukocyte count with a low percentage of lymphocytes and elevated ADA levels in the pleural effusion, which was similar to previous reports [23, 25].

Fig. 1. Pathological findings of NTM pleuritis. HE stain of the pleura obtained by surgical therapy (**a**, **b**) or Ziehl-Neelsen staining (**c**) are shown. **a**, **b** Subpleural epithelial cell granulomas are shown by blue arrows. **c** Ziehl-Neelsen-positive bacillus is shown by a red arrow. NTM, nontuberculous mycobacterium.

Although unclear, the pathogenesis of NTM pleuritis has been considered to be similar to that of tuberculous pleuritis, reported to develop due to leakage or rupture of a subpleural focus, extension of infection from the thoracic lymph nodes, or hematogenous spread [30]. NTM pleuritis may occur via lymphogenous or hematogenous spread in an immunocompromised situation, such as in case of the acquired immunodeficiency syndrome [14, 15] or advanced cancers. However, since NTM is usually less virulent than *M. tuberculosis*, in most cases, the mechanism of NTM pleuritis was primarily suspected to be the perforation of pulmonary NTM disease or spread of inflammation to the pleura [16, 18, 19, 22, 31, 32]. Our study revealed that 73% of cases had subpleural cavitation, and most cases were considered to present bronchopleural fistula or pneumothorax according to the radiological findings. This result supports that NTM pleuritis developed with leakage or perforation of pulmonary NTM disease.

The onset of NTM pleuritis after pulmonary NTM has not been previously reported. Kobashi et al. [26] reported that 7 of 9 cases (67%) were diagnosed with pneumothorax within 1 year after pulmonary NTM. This study revealed that 47% of NTM pleuritis cases occurred within 1 year after the diagnosis of pulmonary NTM, and 27% of patients were diagnosed simultaneously. Although lung lesions preexisted in 11 cases of pleuritis, 6 of them had not been treated with chemotherapy. Treating pulmonary NTM at an early stage can prevent the progression of NTM, such as formation of cavitation, parenchymal destruction, or extension of inflammation to the pleura and development of NTM pleuritis.

The mortality of the pleuritis patients with NTM isolated from pleural effusion was reported as 37–66% at 1 year [25, 26]. A recent report by Park et al. [31] demonstrated that the mortality from NTM pleuritis was 14.3% during a median of 37.4 months of follow-up. They also emphasized the importance of immediate therapy using

a multidisciplinary approach against NTM pleuritis. In this study, the mortality rate of follow-up patients was 17% (2 of 12 cases) at 1 year and 25% (3 of 12 cases) during a mean of 1.8 years of follow-up, which was comparable or better than in the previous studies [25, 26, 31]. Because our cases were younger and had a better performance status than those in the previous studies, drainage and surgical approach could be performed more vigorously, which might have led to a better prognosis of NTM pleuritis.

The current study has several limitations. First, this study was a retrospective analysis of patients from a single institution. The therapeutic regimen or decisions varied depending on the patients' conditions and the clinical experience of the attending physicians. Second, in this retrospective study, the cause of death was based on clinical records of the attending physicians. Although we defined that 2 patients died from NTM pleuritis and 1 patient from other than NTM infection, the precise causes of death could not be verified in the absence of an autopsy. Third, since NTM pleuritis is a rare condition, the number of patients examined in our study is small. This is a case series study and did not include a control group for statistical analysis. Further studies with a much larger number of cases are required to confirm our results.

In conclusion, NTM pleuritis was difficult to treat by medication alone, and the prognosis was poor. In addition to antimycobacterial medications, surgical procedures in the early stages should be considered to treat NTM pleuritis.

Disclosure Statement

The authors declare no conflicts of interest associated with this study.

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Author Contributions

T.A. had full access to the data, takes responsibility for their integrity, and had the final responsibility for the decision to submit the paper for publication. All authors are responsible for the study concept and design. T.A., M.K., H.M., K.T., R.S., N.O., H.N., and K.O. are responsible for acquisition of data. All authors are responsible for analysis or interpretation of data, drafting of the manuscript, and manuscript revision.

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