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Pathologic Findings of Surgically Resected Nontuberculous Mycobacterial Pulmonary Infection

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Background : Surgical resection of the involved lung for nontuberculous mycobacteria (NTM) has become an important curative therapy. However, there is limited information on the histopathological features of NTM pulmonary disease in Korean patients with NTM infection. **Methods :** We evaluated 51 specimens from 49 patients who were treated at our referral center from 2002 to 2009. **Results :** Almost all the cases showed bronchiectasis with lymphocytic infiltration. Variable features of granulomatous inflammation were found; well-defined granulomas in the parenchyma (68.6%), pneumonia-like granulomatous lesions (49.0%) and granulomatous inflammation in the bronchial wall (41.2%) were identified. The microscopic findings of cavitary lesions (37.3%) showed that these lesions were composed of granulomas and necrosis. **Conclusions :** The differentiation of tuberculosis from NTM could not be accurately made based solely on the histological features. However, the airway centered tendency of NTM reflected an airborn etiology, and this could be correlated with the classification according to the radiological findings. In addition, coexisting constitutional lung diseases, and especially bronchiectasis, were suspected to be predisposing conditions for NTM organisms to colonize and progress to true NTM pulmonary disease.

Key Words : Mycobacterium, atypical; Tuberculosis; Lung

There are more than 100 species of the genus Mycobacterium.[1] With the exception of *Mycobacterium tuberculosis* (*M. tuberculosis*) and *M. leprae,* the other members are generally referred to as nontuberculous mycobacteria (NTM). NTMs normally inhabit water and soil, and they are being increasingly recognized as important causes of chronic pulmonary disease, in not only immunocompromised patients, but also among immunocompetent patients.[2] The Korean National Tuberculosis Association has reported more than a thousand new patients with NTM pulmonary disease have been identified in Korea annually since 2002.[3]

For *M. abscessus* pulmonary disease, surgical resection of the involved lung is the only reliable curative therapy.[2,4,5] Patients with NTM disease may require surgical intervention due to other pulmonary morbidities. In some cases, a wedge resection of the suspicious lesion is performed for making the exact diagnosis. However, there is limited information on the histopathological features of NTM pulmonary disease in Korean patients. Therefore, in this study we reviewed the detailed histopathological features of the surgically resected lung specimens from patients with NTM pulmonary disease and who were treated at our referral center.

MATERIALS AND METHODS

From 2002 to 2009, 59 lung specimens from 57 patients who were bacteriologically confirmed to have NTM pulmonary disease by the American Thoracic Society diagnostic criteria were collected at Samsung Medical Center.[6] The five specimens obtained by fine needle biopsy were excluded. Another three patients were excluded because *M. tuberculosis* was also isolated. Finally, 51 specimens from 49 patients were included in this study (Table 1). One patient with Katagener's syndrome (case 20) underwent resection two times; the first procedure was a lobectomy and the second was a segmentectomy. Another patient (case 36) who failed negative conversion on the sputum culture had a second resection of the contralateral lung. The num-

Table 1. Clinical features and course of patients

No.	Sex	Age	Species	Underlying condition	Location (operation)	Follow up
1	F	53	*M. avium*		RLL (lobectomy) and medial segment of RML (segmentectomy)	Recur
2	M	64	*M. intracellulare*	Rheumatoid arthritis	LUL (lobectomy)	DAD
3	F	37	*M. abscessus*		Left (pneumonectomy)	NEAD
4	F	66	*M. abscessus*	Bronchiectasis	RML and RLL (bilobectomy)	Loss
5	M	49	*M. intracellulare*		RUL and RML (wedge resection)	DAD
6	M	32	*M. abscessus*	Hepatitis B virus carrier	RUL (lobectomy)	Loss
7	F	59	*M. abscessus*		Left (pneumonectomy)	NEAD
8	F	45	*M. abscessus*	Aspergilloma	RUL (lobectomy)	NEAD
9	M	62	*M. avium*		RUL (lobectomy)	NEAD
10	M	66	*M. xenopi*	Pneumothoranx	RLL (lobectomy)	DAD
11	F	49	*M. intracellulare*	Sjogren syndrome, usual interstitial pneumonia	RLL (lobectomy)	NEAD
12	F	45	*M. intracellulare*		Left (pneumonectomy)	Recur
13	F	53	*M. abscessus*		RUL (lobectomy)	Recur
14	F	50	*M. abscessus*	Bronchiectasis	RML (lobectomy)	NEAD
15	F	50	*M. avium*	Bronchiectasis	LLL (lobectomy)	NEAD
16	M	63	*M. intracellulare*		RUL (lobectomy)	NEAD
17	F	50	*M. intracellulare*		LUL (wedge resection)	NEAD
18	M	58	*M. abscessus*	Hepatitis C virus carrier	LLL (lobectomy) and lingular segment of LUL (segmentectomy)	NEAD
19	F	37	*M. intracellulare*	Bronchiectasis	Posterior basal segment of RLL (segmentectomy)	NEAD
20	F	25	*M. abscessus*	Katagener's syndrom, status inversus totalis	RML (lobectomy) Lingular segment of LUL (segmentectomy) and anteromedial basal segment of RLL (segmentectomy)	PAD PAD
21	F	41	*M. intracellulare*		RUL (lobectomy) and superior segment of RLL (segmentectomy)	NEAD
22	M	44	*M. intracellulare*	Recurrent pneumothorax	RUL and RML (bilobectomy)	Loss
23	F	25	*M. abscessus*	Otitis media	RML (lobectomy)	NEAD
24	M	28	*M. intracellulare*		Posterior segment of RUL (segmentectomy)	NEAD
25	F	40	*M. abscessus*	Fungal sinusitis	RML (segmentectomy) and superior segment of RLL (segmentectomy)	Recur
26	F	34	*M. abscessus*	Papillary carcinoma of thyroid	RML and RLL (bilobectomy)	NEAD
27	M	61	*M. abscessus*		RUL and RML (bilobectomy) and superior segment of RLL (segmentectomy)	Recur
28	M	34	*M. intracellulare*		Apicoposterior segment of LUL (segmentectomy)	NEAD
29	F	69	*M. intracellulare*	Thyroid cancer	RUL (lobectomy) and RML (wedge resection)	PAD
30	M	64	*M. intracellulare*	Pneumothoranx	RUL (lobectomy)	Loss
31	M	21	*M. avium*		RUL (lobectomy)	NEAD
32	M	33	*M. avium*	Pulmonary sequestration	RLL (lobectomy)	NEAD
33	F	63	*M. abscessus*	Bronchiectasis	RML (lobectomy)	NEAD
34	M	9	*M. avium*		Apicoposterior segment of LUL (segmentectomy)	NEAD
35	F	34	*M. abscessus*		Basal segment of LLL (segmentectomy)	PAD
36	M	45	*M. avium*	Diabetes mellitus	Apicoposterior and anterior segments of LUL (segmentectomy) RUL (lobectomy)	PAD NEAD
37	F	27	*M. abscessus*		LLL (lobectomy)	NEAD
38	M	40	*M. abscessus*		RUL and RML (bilobectomy)	NEAD
39	F	47	*M. intracellulare*	Bronchiectasis, carcinoid of rectum	RML (lobectomy), posterior segment of RUL (segmentectomy) and superior segment of RLL (segmentectomy)	NEAD
40	F	49	*M. intracellulare*		RLL (lobectomy)	NEAD
41	F	48	*M. intracellulare*		Left (pneumonectomy)	PAD
42	F	36	*M. celatum*		LUL (lobectomy) and superior segment of LLL (segmentectomy)	NEAD
43	F	56	*M. fortuitum*		RML (lobectomy)	NEAD
44	M	58	*M. intracellulare*	Diabetes mellitus	Right (pneumonectomy)	DAD
45	F	46	*M. abscessus*		Lingular segment of LUL (segmentectomy)	PAD
46	F	42	*M. abscessus*	Katagener's syndrom, status inversus totalis	LUL and LML (bilobectomy)	PAD
47	F	50	*M. intracellulare*	Advanced gastric carcinoma	LUL (lobectomy)	PAD
48	F	28	*M. avium*		RUL (lobectomy) and superior segment of RLL (segmentectomy)	PAD
49	M	70	*M. intracellulare*	Subtotal gastrectomy	RML (lobectomy)	PAD

F, female; M, mycobacterium; RLL, right lower lobectomy; LUL, left lower lobectomy; DAD, Disease associated death; NEAD, no evidence of active disease; RUL, right upper lobectomy; LLL, left lower lobectomy; PAD, persistent active disease; LML, left middle lobectomy; RML, right middle lobectomy.

ber of specimens in each category is listed by the surgical procedure (Table 1).

All the tissues were fixed in 10% buffered formalin and the representative sections were embedded in paraffin. The hematoxylin and eosin (H&E) stained slides were reviewed by an experienced pathologist. In some cases, Ziehl-neelson stain or Grocott's methemanine silver stain was performed on selected slides. In eight cases, polymerase chain reaction (PCR) was performed on the formalin-fixed, paraffin-embedded blocks. Case 2 had undergone the AMPLICOR Mycobacterium tuberculosis test (Roche, Madison, WI, USA) in 2003, and the other cases (cases 6, 19, 31, 32, 34, 36, and 47) had undergone AMSOLUTETM MTB PCR (biosewoom, Seoul, Korea) since 2004.

The medical records were reviewed for age, a history of diagnosed or treated tuberculosis, the biologically confirmed NTM species, the surgical procedures and the prognosis. All the acceptable medical images of the gross specimens were also reviewed.

RESULTS

Clinical features (Table 1)

The age of the patients at the time of surgical intervention ranged from 9 to 70 (median, 47 years). The number of male and female patients was 19 (38.8%) and 30 (61.2%), respectively. The most commonly isolated species were *M. abscessus* (19 patients, 38.8%) and *M. intracellulare* (19 patients, 38.8%). *M. avium* was identified in eight patients (16.3%). Three uncommon species, *M. xenopi, M. celatum*, and *M. fortuitum* were identified in three cases (cases 13, 47, and 48). Most of the patients were diagnosed with NTM pulmonary disease before surgery, but in one case that was suspicious for pulmonary tuberculosis, the definitive result from culture was reported after the surgical procedure (case 2), and in two cases, evaluations for NTM were performed based on the histopathology after surgery (cases 5 and 9). Other lung morbidities, infectious or constitutional disorders, or systemic disease were present in some cases.

Except for four cases that were lost to follow up, the clinical follow-up data of 45 patients was available for this study. Four patients died of their NTM pulmonary infections within two months after surgery. The results of the NTM sputum cultures were conversion to negative after surgery in 31 patients (68.9%). Among them, five patients were diagnosed with recurrent NTM pulmonary disease by the return to positive results on sputum cultures. The remaining 26 patients were relieved from their symptoms, such as cough and sputum production, and they had no evidence of NTM infection. Unfortunately, the NTM species were continuously isolated in the sputum of 10 patients (22.2%). A patient (case 36) who did not show negative conversion after the first segmentectomy of the left upper lobe underwent a second resection of the right upper lobe, and then the sputum culture was converted to negative. However, another patient with Katagener's syndrome and who underwent resection two times (case 20) showed a persistent NTM infection that was proven by sputum culture.

Histopathological features (Table 2)

Bronchiectasis

At least 30 specimens from 29 patients had grossly identified bronchiectasis (Figs. 1C, E, 2A). In two cases among them (cases 16 and 19), saccular bronchiectasis that looked like a cavity was identified. In two cases (cases 33 and 43), bronchiectasis with peribronchial inflammation was the only pathological finding and no granulomatous lesions were noted.

Granulomatous reactions

Cavitary lesions with yellow to gray friable necrotic changes that destroyed the bronchus or lung parenchyma were found in 19 specimens (Fig. 1A, B). Microscopic examination revealed that the walls of the cavities were composed of conglomerated granulomas with epithelioid histiocytes. The luminal portions of the cavity resulted from caseous necrosis of the large granulomas. In one case with *M. abscessus* infection (case 13), the entire right upper lobe was a unilocular cyst with fibrotic and calcified walls.

Table 2. Histopathologic features of specimens

Histologic features	No. of specimens	%
Well-defined granuloma in parenchyma	35	68.6
Near-totally calcified granuloma	1	2.0
Grossly identifiable bronchiectasis	30	58.8
Pneumonia-like granulomatous lesion	25	49.0
Pneumonia-like granulomatous lesion as a main feature	5	9.8
Granulomatous inflammation in bronchial wall	21	41.2
Cavitary lesion	19	37.3
Gradient connection between the cavity and bronchi	10	19.6
Unilocular fibrotic cyst	1	2.0
Bronchiectasis only	2	3.9
Granulomas in peribronchial lymph nodes	10	19.6
Peribronchial lymph nodes with totally calcified change	1	2.0
Neutrophilic abscess in peribronchial lymph nodes	1	2.0

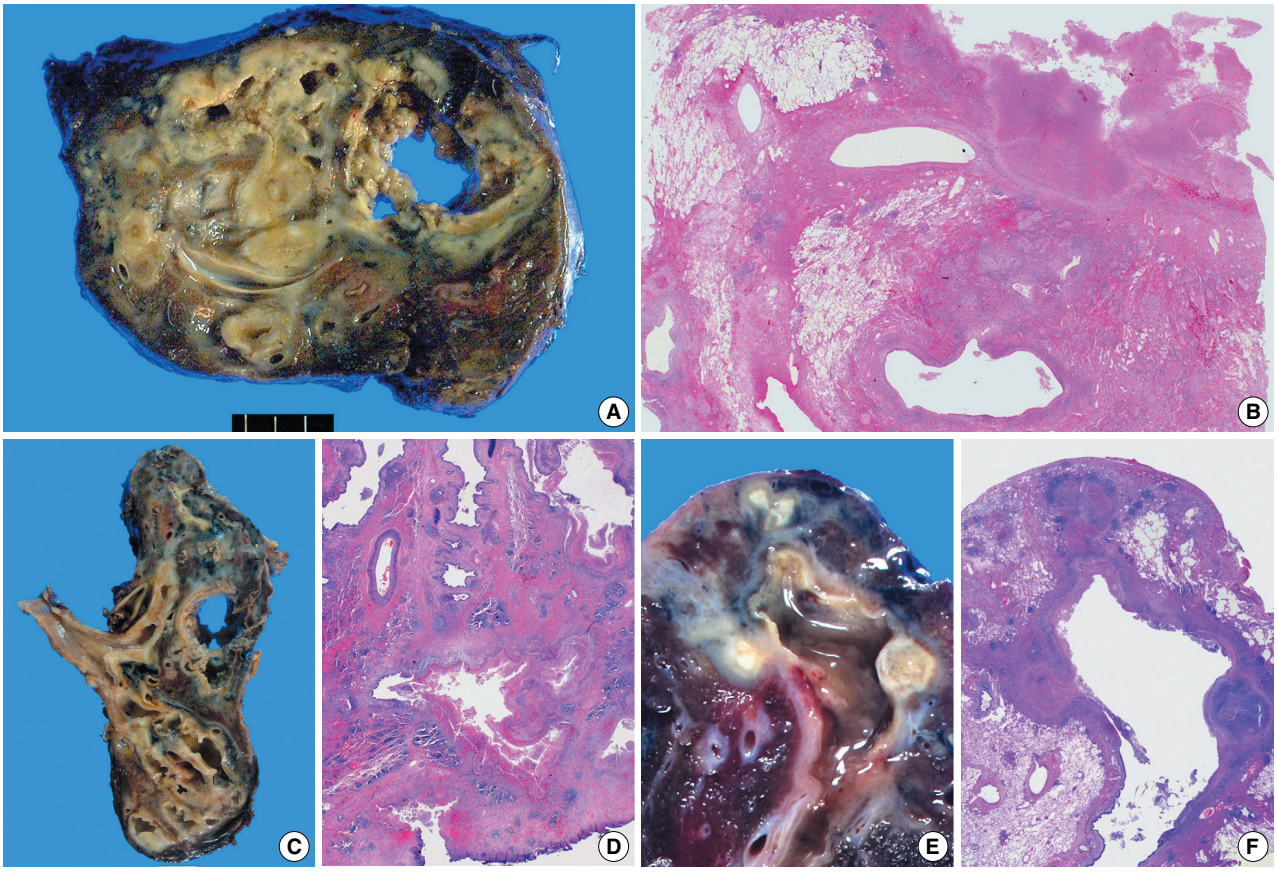

Fig. 1. Gross photographs and close-views of microscopic slides of *Mycobacterium abscessus* pulmonary infection show caseating granulomatous inflammation and cavity formation where are direct connections with dilatated bronchi (A, B). Pneumonectomy specimen shows severely destroyed lung with saccular and cylindrical bronchiectasis with caseating granulomas in bronchial wall (C-F).

In 35 specimens, variable sized well-defined granulomas with/without definite cavitary lesions were present in the lung parenchyma (Fig. 2A-D). In some granulomas the central portion was necrotic; there was more frequent central caseous necrosis in the larger granulomas. One case had a near-total calcified granuloma (Fig. 2B inset).

Granulomatous inflammation in the bronchial walls was also found in 21 specimens. The involved bronchi revealed small granulomas in the epithelial or muscular layer of the bronchi, with variable degrees of lymphocytic infiltration (Fig. 1C-F). Among the cases with cavitation or definitely dilated bronchi with granulomatous reaction, 10 cases had microscopically identifiable gradient connections by the granulomatous inflammation between the main lesion and the relatively preserved bronchi (Fig. 1B). Whether definite granulomas were present or not, almost all the bronchi in the specimens showed chronic inflammation with lymphocytic infiltration and fibrotic changes of the walls (Fig. 2E, F).

Pneumonia-like granulomatous lesions with ill-defined granulomas, epithelioid cells and fibroblastic interstitial reaction were identified in 25 cases (Fig. 2G, H). This type of lesion could be found locally in the lung parenchyma among the definite granulomas or extensively all around the specimen. In five cases (cases 5, 8, 19, 20, and 47), the pneumonia-like granulomatous lesion was the main histopathological feature without any definite granulomas.

Peribronchial lymph nodes

Evaluations for the peribronchial lymph nodes were possible in 37 cases. Granulomas were found in 10 cases. The granulomas in the peribronchial lymph nodes usually had non-caseating features. The lymph nodes in three cases showed hyalinized nodules and those in one case showed totally calcified changes. Peculiar neutrophilic abscesses were found in one case (case 5). A case with coexistent primary adenocarcinoma of the lung (case 44) showed metastatic carcinoma in the peribronchial lymph nodes.

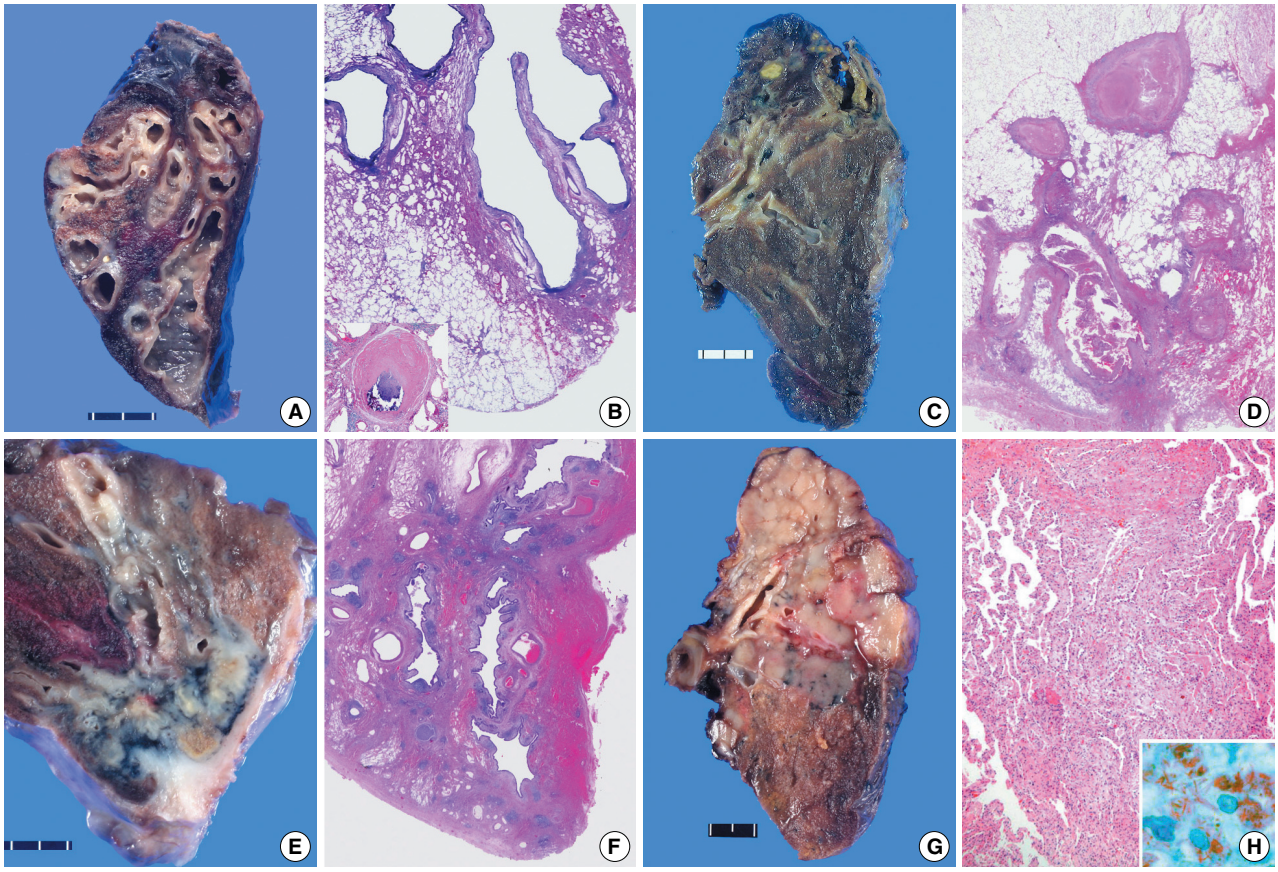

Fig. 2. Various forms of nontuberculous mycobacterial pulmonary infection include mainly bronchiectatic form with a small calcifying granuloma (A, B with inset; *Mycobacterium abscessus* [*M. abscessus*]), and parenchymal discrete granulomas (C, D; *M. intracellulare* infection), bronchiectasis with bronchopneumonia with a few granuloma (E, F; *M. abscessus*), and granulomatous pneumonia (G, H; *M. intracellulare*) with many acid-fast bacilli-positive bacilli in alveolar exudate (inset in H).

Table 3. Histologic features along specific nontuberculous mycobacteria species

Histologic features	*M. abscessus* (%)	*M. avium* complex (%)	
		M. intracellulare	*M. avium*
Bronchiectasis	17/20 (85.0)	9/19 (47.4)	2/9 (22.2)
Granulomatous inflammation in bronchial wall	11/20 (55.0)	7/19 (36.8)	3/9 (33.3)
Granulomas in parenchyma	11/20 (55.0)	13/19 (68.4)	9/9 (100)
Pneumonia-like granulomatous lesion	9/20 (45.0)	11/19 (57.9)	3/9 (33.3)
Cavitary lesion	5/20 (25.0)	7/19 (36.8)	6/9 (66.7)

M, mycobacterium.

Histology of specific NTM species (Table 3)

In the 48 specimens with three major specific NTM species, the proportions of bronchiectasis and the histological features of granulomatous inflammation were evaluated. The specimens infected by the *M. avium* complex (MAC), including *M. intracellulare* and *M. avium*, showed a more frequent tendency for parenchymal granulomas and cavitary lesions than that for the specimens infected with *M. abscessus*. On the other hand, *M. abscessus* tended to be associated with bronchiectasis and bronchial granulomatous lesions.

Additional pathology findings

Aspergillomas were found in four cases. The fungal balls were located in the cavity of the granulomas or in the bronchiectatic bronchi. Bronchogenic cysts were found in three cases. Among them, the specimens of two cases revealed multiple parenchymal granulomas and endobronchial granulomatous inflammation, but one case (case 33) just showed grossly and microscopi-

cally confirmed bronchiectasis and bronchial inflammation without granulomatous reaction. Bullae, pulmonary sequestration, actinomycosis and primary pulmonary adenocarcinoma were found in one case each.

Additional studies

Ziehl-Neelsen staining was performed in 19 cases and acid-fast bacilli were identified in 13 cases. The bacilli usually were found in the large granulomas with caseous necrosis, but in two cases (case 19 and 20), they were identified in the secretion and not in the parenchyma (Fig. 2H inset). PCR for *M. tuberculosis* was negative in seven out of eight cases. One case (case 2) had a positive result.

DISCUSSION

In this study, there were more specimens from female patients than from male patients. In Korea, the ratio of male to female cases in the newly identified patients is 1.2 to 1.7 annually.[3] This discordance might be due to a selection bias; for example, exclusion of coinfection with tuberculosis. The most commonly isolated NTM organism in Korea is *M. intracellularae.*[3] However, in this study, not only *M. intracellularae*, but also *M. abscessus* were the most frequently confirmed organisms. The treatment for each species may be different. For *M. abscessus* infection, surgical treatment is preferred to medical treatment, with medical treatment being the principle management of infections caused by other species.[5]

Although NTM pulmonary disease is generally known to be slowly progressive, 4 out of 49 (8.2%) patients died as a consequence of progressive lung disease and respiratory failure. Griffith *et al.*[4] also reported a 14% disease associated mortality rate for the patients with NTM.

The differentiation of tuberculosis from NTM cannot be accurately made based solely on the histological features. The classical "tuberculosis-like" granulomatous reaction is the most common histological pattern observed in patients with NTM pulmonary infections.[7] However, the NTM infected lesions more commonly show an airway centered tendency.[8] In this study, many of the specimens had definite bronchial lesions that showed granulomas in the bronchial walls. The cavitary lesions associated with NTM pulmonary infections are thought to develop from bronchial lesions.[9] The progression from bronchial granulomatous lesions to cavitary lesions noted in this study supports this suggestion. The airway-related distribution of lesions was well correlated with the airborne spread of NTM as the etiology of disease. On the other hand, granulomas in the parenchyma were also an important histological feature found in many cases. In addition, connections with small airways were also found in a few cases with parenchymal granulomas.

Pneumonia-like granulomatous lesions are on the spectrum of granulomatous inflammatory reactions. Variable sized pneumonia-like granulomatous lesions can be commonly observed in the periphery of large granulomas or among discrete nodules. A pneumonia-like granulomatous lesion that filled the entire specimen was the only pathological feature in one unique case (case 5). The prognosis of this patient was poor, and he died soon after the diagnosis. Another case with disease-associated death (case 10) showed mainly pneumonia-like granulomatous reaction with a few scattered small granulomas in the parenchyma. However, the pneumonia-like granulomatous lesions were not the reason for the patient's poor prognosis. Two cases with extensive endobronchial and parenchymal granulomas (cases 2 and 44) also had disease-associated death and the other cases with mainly pneumonia-like granulomatous lesions had a good prognosis.

Fujita *et al.*[10] reported that mycobacteria were found only in the necrotic tissue of the inner surface of the cavitary wall, although extensive granulomas throughout the airway were observed. In present study, there were two cases with acid-fast bacilli only in the secretion. The main histological features in these cases were bronchiectasis without definite granulomas and mild pneumonia-like granulomatous lesions. One of the patients had persistent NTM-positive sputum even after surgery.

On the other hand, in another two cases (cases 33 and 43), the only pathological feature was bronchiectasis, with neither a granulomatous reaction nor confirmed acid-fast bacilli. In both cases, the post-operative results of the sputum culture for NTM were converted to negative.

Dividing the histological features by the species has helped to correlate the histological features with the clinical and radiological findings. MAC pulmonary disease has been differentiated into two subtypes; an upper lobe cavitary form and a nodular bronchiectatic form.[11] The former is the more common and it is the widely known presentation of MAC pulmonary disease. In the present study, the specimens associated with MAC also showed frequent cavity formation. On the other hand, high-resolution computed tomography of the lung with *M. abscessus* frequently shows associated cylindrical bronchiectasis and multiple small nodules, and cavitation occurs in only approximately

15% of these cases.[4] Frequent bronchiectasis and bronchial lesions were observed on the radiology and the histology of the *M. abscessus* specimens in this study. However, the radiological findings associated with *M. Abscessus* were similar to those associated with the nodular bronchiectatic form of MAC pulmonary disease. The results of the present study showed that bronchiectasis and a wide ranging spectrum of granulomatous inflammation were found in the specimens from all the species. Therefore, there was no distinguishing characteristic of any given species.

Many patients had a previous history of constitutional lung disease and especially bronchiectasis. Bronchiectasis is thought to predispose patients to NTM colonization and progression to true NTM pulmonary disease. A bronchogenic cyst can also increase the susceptibility to NTM colonization. In addition, aspergillosis and actinomycosis were also found in some cases. Most of the additional organisms were not suspected preoperatively. Therefore, careful gross and microscopic examinations are required to evaluate for possible coexisting non-mycobacterial species. The results of the PCR for *M. tuberculosis* should be negative for making a diagnosis of NTM disease. However, with a positive result, tuberculosis must then be confirmed bacteriologically on other specimens such as sputum or the bronchoalveolar lavage fluid. Case 2, which had positive PCR results for *M. tuberculosis*, was confirmed as NTM on culture and on isolation from the sputum.

In conclusion, the results of this study provide pathologists additional information on the histological features of NTM. Further studies are needed for determining the clinical, radiological and histological correlations and their association with the outcomes of patients who suffer with NTM.

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