Review

Prevalence of systemic and local risk factors for pulmonary non-tuberculous mycobacterial disease in Japan: a single-institution study

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Abstract

Objective: To identify the prevalence of risk factors for pulmonary non-tuberculous mycobacterial (NTM) disease in a Japanese population.

Patients and Methods: We reviewed 337 consecutive Japanese patients (210 women) with pulmonary NTM disease, including 225 patients with Mycobacterium avium complex (MAC) disease (95.8%) at our hospital during 2006–2017. We calculated the prevalence of risk factors reported in Western countries among mycobacterial species.

Results: Pulmonary MAC disease cases comprised 78.2% of pulmonary NTM patients in their 40s, increasing to 100% at age ≥80 years. Body mass index (BMI) was <18.5 in approximately 40% of patients, which was significantly higher than the prevalence of underweight in the Japanese population. The percentage of male heavy smokers (Brinkman index ≥600) was 58.2% of pulmonary NTM disease and was high for all mycobacterial species. In pulmonary MAC disease, systemic factors were observed in the order of malignant tumors (other than lung cancer), diabetes, rheumatoid arthritis, and tuberculosis. Local factors were observed in the order of bronchiectasis, chronic obstructive pulmonary disease, lung cancer, and bronchial asthma.

Conclusion: The risk factors reported in Western countries were relatively highly prevalent among Japanese pulmonary NTM disease patients. This observation may help elucidate disease onset mechanisms.

Key words: non-tuberculous mycobacteria, epidemiology, risk factor, aging, gender

Introduction

The number of individuals with non-tuberculous mycobacteria (NTM) is increasing globally. Increased incidence has been reported in the United States, Canada, and Australia, and in East Asia in recent years[1]. A similar trend has been observed in Japan, and an epidemiological study conducted by the Ministry of Health, Labour and Welfare showed that the estimated prevalence increased from 14.7 per 100,000 population in 2014 to 5.7 per 100,000 population in 2007[2]. Of the total pulmonary NTM disease incidence, 88% were pulmonary Mycobacterium avium complex (MAC) disease, 4.3% were pulmonary *M. kansasii* infection, 3.3% were pulmonary *M. Abscessus* infection, and 3.6% were other infections. It is urgently necessary to identify the status of pulmonary NTM diseases, including pulmonary MAC disease.

NTM species are widely distributed in the natural environment and have been detected in several sources, including tap water. Humans are similarly exposed to NTM in an ordinary living environment; for example, the proportion of healthy Japanese people who tested positive in the *M. intracellulare* tuberculin test was reported to be as high as 21.9% between the ages of 20 and 29 years, 20.5% between 30 and 39 years, and 32.1% between 40 and 53 years[3]. However, only a small proportion of infected individuals develop pulmonary NTM disease, and individual host variation is

suggested to be closely related to disease onset, which often occurs in old age after a long period of infection. In recent years, however, the incidence of pulmonary NTM disease has notably increased globally, and it is therefore crucial to determine the mechanisms of disease onset.

Decreased systemic and local immune capacities are considered risk factors for the onset of pulmonary NTM disease, but the underlying mechanism remains unknown. Systemic factors that have been reported as risk factors for disease onset in Western countries include female sex, old age, underweight, diabetes, history of rheumatoid arthritis treated with tumor necrosis factor inhibitors, history of tuberculosis, and acquired immunodeficiency syndrome[1]. Reported local factors include bronchiectasis (BE), chronic obstructive pulmonary disease (COPD), thoracic disorders, and lung cancer[1]. In Japan, decreased levels of peripheral lymphocytes (<1,500/μL) and underweight (body mass index [BMI] <18.0 kg/m^2) in patients with rheumatoid arthritis were shown to be related to the onset of pulmonary MAC disease[4]. However, few studies have reported the risk factors in individuals.

To further understand the status of pulmonary NTM disease, we investigated the prevalence of disease-onset risk factors, which were previously reported in Western countries, in 337 consecutive patients encountered over approximately 12 years in Jichi Medical University Hospital.

Materials and Methods

Study population

We retrospectively reviewed the medical records of 337 consecutive patients newly diagnosed with pulmonary NTM disease at the Jichi Medical University Hospital (Tochigi Prefecture, East Japan) between January 2006 and August 2017. We extracted 6,286 respiratory specimens (sputum, bronchoalveolar lavage fluid (BALF), or lung biopsy specimen) positive for acid-fast bacteria in our hospital during the study period. Those that matched the 2008 diagnostic criteria of The Japanese Society for Tuberculosis and The

Japanese Respiratory Society with radiological, pathological, laboratory, and bacteriological findings were diagnosed with pulmonary NTM disease. We evaluated age, BMI, smoking status, and past medical history and calculated the prevalence of systemic and local risk factors for pulmonary NTM disease reported in Western countries according to causative mycobacterial species.

This study was reviewed and approved by the Jichi Medical University Ethics Committee in the form of "Substituting an opt-out consent form (posted on the website)" (No. Rin-A18-015, June 11, 2018).

The 2008 Japanese guideline

The diagnostic criteria in the "Guideline for Diagnosis of Non-Tuberculous Acid-Fast Bacterial Infection of the Lung-2008"[5] by the Japanese Society for Tuberculosis and the Section on Tuberculosis and Infection of the Japanese Respiratory Society are in agreement with the concepts of the official American Thoracic Society/Infectious Diseases Society of America statement[6].

Statistical analysis

Categorical data are presented as absolute numbers and relative frequencies (n, %).

Results

The study population consisted of 127 men and 210 women. Figure 1 shows the distribution of pulmonary NTM disease cases according to the age group at diagnosis. The age distribution showed a monophasic pattern in both men and women, with a peak at age 70–79 years in men and age 60–69 years in women.

Detected mycobacterial species

Table 1 shows the number and percentage of patients with the causative mycobacterial species. Two hundred twenty-five patients were infected with pulmonary *M. avium* infection (66.8%), 98 with *M. intracellulare* (29%),
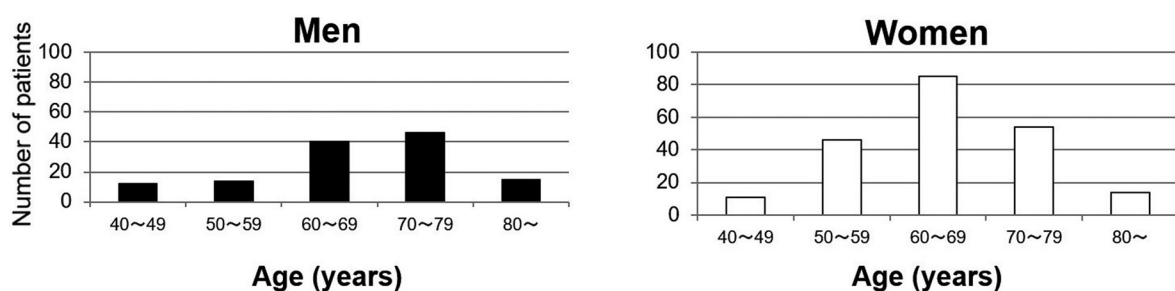

Figure 1 Distribution of pulmonary non-tuberculous mycobacterial disease cases based on age group at diagnosis.
Age distribution shows a monophasic pattern in both men and women, with a peak at age 70–79 years in men and age 60–69 years in women.

Table 1 Number and percentage of patients based on sex and causative mycobacterial species

Mycobacterial species	Total, n (%)	Men, n (%)	Women, n (%)
M. avium	225 (66.8)	73 (57.5)	152 (72.4)
M. intracellulare	98 (29.0)	44 (34.6)	54 (25.7)
M. kansasii	8 (2.3)	7 (5.5)	1 (0.5)
M. chelonae	3 (0.9)	1 (0.8)	2 (1.0)
M. abscessus	2 (0.6)	1 (0.8)	1 (0.5)
M. gordonae-like	1 (0.3)	1 (0.8)	0 (0.0)

8 with *M. kansasii* (2.3%), 3 with *M. chelonae*, 2 with *M. abscessus*, and 1 with *M. gordonae-like*. MAC disease is highly prevalent in both men and women. However, pulmonary *M. avium* and pulmonary *M. intracellulare* infection accounted for 72.4% and 25.7% of the cases in women, and 57.5% and 34.6% of the cases in men, respectively. Moreover, pulmonary *M. kansasii* infection accounted for 5.5% of the cases in men.

Overall, 78.2% of the patients in their 40s had pulmonary MAC disease, which increased with age and reached 100% at age ≥80 years (Figure 2). The percentage of patients with pulmonary *M. intracellulare* infection increased consistently with age, although this reflected an aging-associated increase among men. No aging-associated increase was observed in the percentage of pulmonary *M. avium* infection.

Pulmonary *M. kansasii* infection was observed in both middle-aged men and women; it was found in 33.3% of men in their 40s and 28.6% of men in their 50s (Figure 2). Pulmonary *M. chelonae* infection was observed in both men and women in their 40s and 60s.

Body mass index

The percentage of underweight patients with BMI <18.5 was investigated. Among all cases of pulmonary NTM disease, the BMI was <18.5 in 40.4% of men and 40.0% of women (Table 2), which was significantly higher than the prevalence of underweight in the Japanese population. The 2016 National Health and Nutrition Survey showed that BMI was <18.5 in 4.7% of men and 12.7% of women, between 18.5 and 25 in 56.2% of men and 76.3% of women, and ≥25 in 31.1% of men and 19.0% of women. The percentages of patients with BMI <18.5, according to the Mycobacterium species, were 47.5% of men and 41.1% of women with pulmonary *M. avium* infection, 26.9% of men and 39.4% of women with pulmonary *M. intracellulare* infection, and 28.6% of men with pulmonary *M. kansasii* infection (Table 2).

Smoking status

The percentage of patients without a history of smoking (Brinkman Index (BI) = 0) was calculated. Among men, the

Table 2 Number and percentage of patients based on BMI and causative mycobacterial species

	BMI	<18.5	18.5–25	25≤
Total	Total	88 (40.2)	115 (52.5)	16 (7.3)
	Men	38 (40.4)	49 (52.1)	7 (7.4)
	Women	50 (40.0)	66 (52.8)	9 (7.2)
M. avium	Total	65 (43.6)	72 (48.3)	12 (8.1)
	Men	28 (47.5)	27 (45.8)	4 (6.8)
	Women	37 (41.1)	45 (50.0)	8 (8.9)
M. intracellulare	Total	20 (33.9)	36 (61.0)	3 (5.1)
	Men	7 (26.9)	17 (65.4)	2 (7.7)
	Women	13 (39.4)	19 (57.6)	1 (3.0)
M. kansasii	Total	2 (28.6)	4 (57.1)	1 (14.3)
	Men	2 (28.6)	4 (57.1)	1 (14.3)
	Women	0 (0.0)	0 (0.0)	0 (0.0)

BMI: body mass index (kg/m^2).

proportion of never-smokers was 22.6% of all pulmonary NTM disease cases, 25.6% of those with pulmonary *M. avium* infection, 21.4% of those with pulmonary *M. intracellulare* infection, and 14.3% of those with pulmonary *M. kansasii* infection (Table 3). Among women, the proportion of never-smokers was 87.0% of all pulmonary NTM diseases, 83.4% of those with pulmonary *M. avium* infection, and 96.2% of those with pulmonary *M. intracellulare* infection.

The percentage of patients who were heavy smokers (BI ≥600) was then identified. In men, this proportion was 58.2% of the total pulmonary NTM disease cases, 62.5% of those with pulmonary *M. avium* infection, 52.4% of those with pulmonary *M. intracellulare* infection, and 57.2% of those with pulmonary *M. kansasii* infection. Among women, the proportion of heavy smokers was 3.9% of all pulmonary NTM disease cases, 4.7% of those with pulmonary *M. avium* infection, and 1.9% of those with pulmonary *M. intracellulare* infection (Table 3).

Smoking has been identified as a risk factor for disease onset in pulmonary *M. kansasii* infection[7], but our results showed that a similar smoking history was observed in men with pulmonary MAC disease.
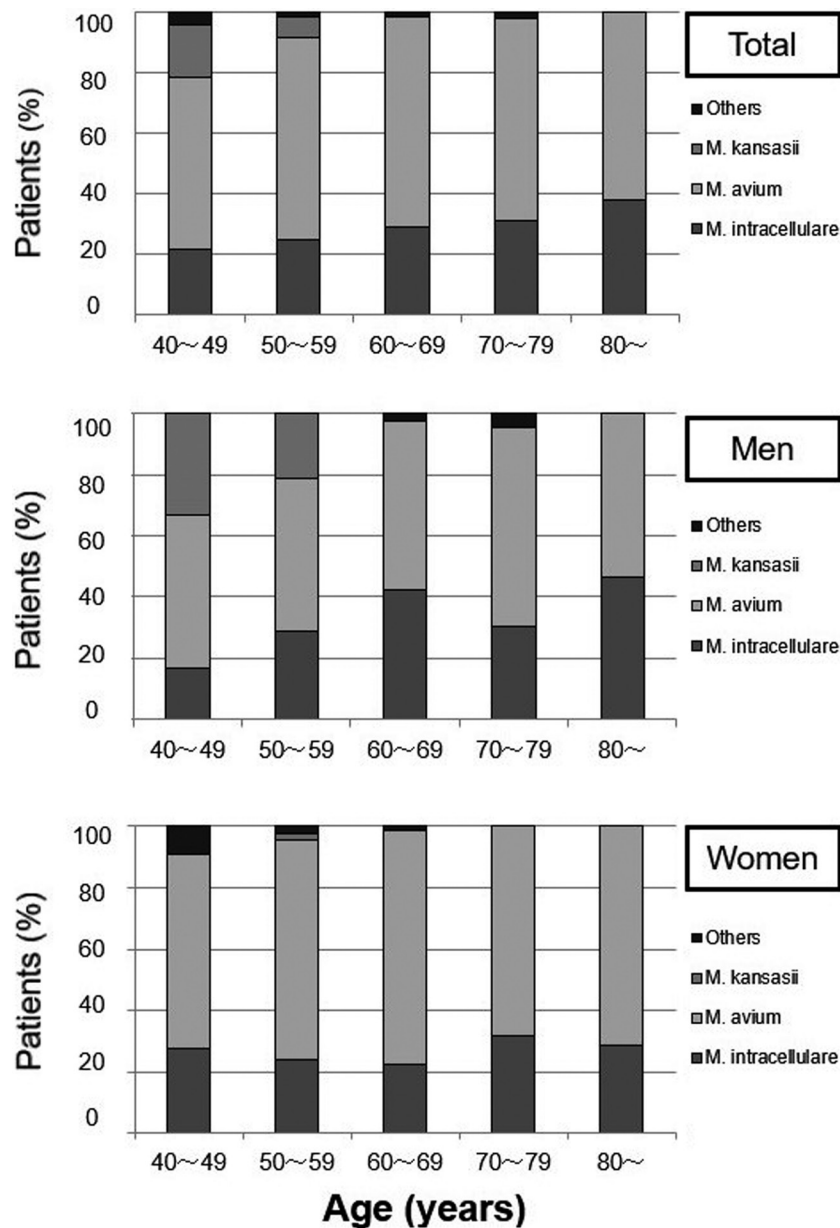
Figure 2 Breakdown of detected species according to patient age.
Overall, 78.2% of patients in their 40s had pulmonary mycobacterium avium complex (MAC) disease, which increased with age and reached 100% at age ≥80 years. The percentage of patients with pulmonary *M. intracellulare* infection increased consistently with age, although this reflected an aging-associated increase among men. Pulmonary *M. kansasii* infection was found in 33.3% of men in their 40s and in 28.6% of men in their 50s.

Past medical history

The percentage of patients with a medical history of disorders, identified as risk factors in Western countries, was also investigated. In all pulmonary NTM disease cases, the percentages of patients with systemic factors were as follows: 21.1% with malignant tumors (other than lung cancer), 13.9% with diabetes, 9.5% with rheumatoid arthritis, 5.0% with tuberculosis, and 1.5% with human immunodeficiency virus/acquired immunodeficiency syndrome. Similarly, the percentages of those with local factors were as follows: 20.2% with BE, 12.5% with COPD, 4.5% with lung cancer, 4.2% with bronchial asthma, and 3.9% with pneumothorax (Figure 3). A similar prevalence was observed for pulmonary MAC disease, and the results were thought to reflect

Table 3 Number and percentage of patients based on smoking status and causative mycobacterial species

	BI	0	0–400	400–600	600–1,000	1,000≤
Total	Total	207 (64.1)	29 (9.0)	12 (3.7)	35 (10.8)	40 (12.4)
	Men	26 (22.6)	17 (14.8)	5 (4.3)	29 (25.2)	38 (33.0)
	Women	181 (87.0)	12 (5.8)	7 (3.4)	6 (2.9)	2 (1.0)
M. avium	Total	142 (66.0)	18 (8.4)	8 (3.7)	23 (10.7)	24 (11.2)
	Men	16 (25.0)	7 (10.9)	1 (1.6)	17 (26.6)	23 (35.9)
	Women	126 (83.4)	11 (7.3)	7 (4.6)	6 (4.0)	1 (0.7)
M. intracellulare	Total	60 (63.2)	9 (9.5)	3 (3.2)	9 (9.5)	14 (14.7)
	Men	9 (21.4)	8 (19.0)	3 (7.1)	9 (21.4)	13 (31.0)
	Women	51 (96.2)	1 (1.9)	0 (0.0)	0 (0.0)	1 (1.9)
M. kansasii	Total	2 (25.0)	1 (12.5)	1 (12.5)	2 (25.0)	2 (25.0)
	Men	1 (14.3)	1 (14.3)	1 (14.3)	2 (28.6)	2 (28.6)
	Women	1 (100.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)

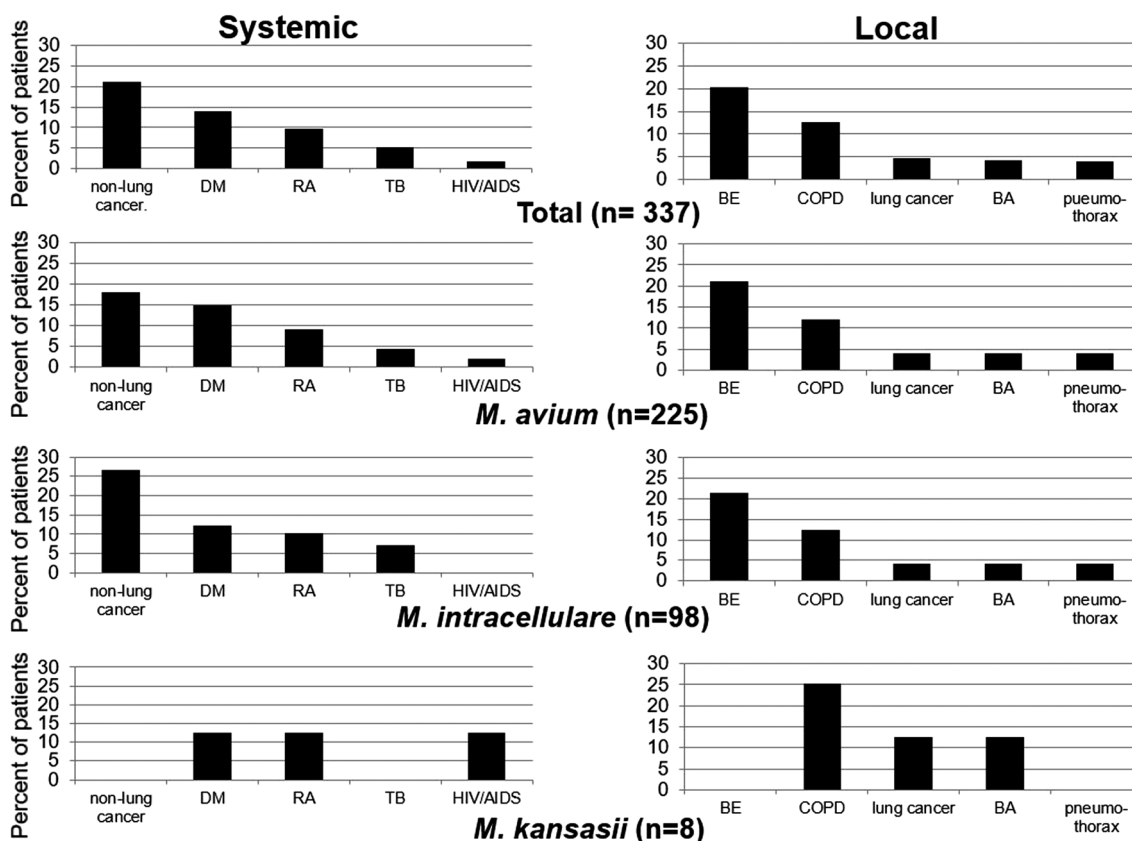BI: Brinkman Index = number of cigarettes per day × number of years smoking.

Figure 3 Systemic and local risk factors for pulmonary non-tuberculous mycobacterial disease according to the mycobacterial species. In all pulmonary non-tuberculous mycobacterial (NTM) disease cases, the percentages of patients with systemic factors were as follows: 21.1% with malignant tumors (other than lung cancer), 13.9% with DM, 9.5% with RA, 5.0% with TB, and 1.5% with HIV/AIDS. Similarly, the percentages of those with local factors were as follows: 20.2% with BE, 12.5% with COPD, 4.5% with lung cancer, 4.2% with BA, and 3.9% with pneumothorax. A similar prevalence was observed for pulmonary mycobacterium avium complex (MAC) disease. In contrast, malignant tumors (other than lung cancer) and BE were not observed in those with pulmonary *M. kansasii* infection. A relatively high percentage of patients had COPD (25%).
DM: diabetes mellitus; RA: rheumatoid arthritis; TB: tuberculosis; HIV/AIDS: human immunodeficiency virus/acquired immunodeficiency syndrome; BE: bronchial ectasia; COPD: chronic obstructive pulmonary disease; BA: bronchial asthma.

this. In contrast, malignant tumors (other than lung cancer) and BE were not observed in those with pulmonary *M. kansasii* infection. A relatively high percentage of the patients had COPD (25%; Figure 3).

Discussion

This epidemiological study investigated the prevalence of various systemic and local risk factors that were previously reported in Western countries, in Japanese patients with pulmonary NTM disease, according to the mycobacterial species. Four important findings were obtained. First, among all patients with pulmonary NTM disease, pulmonary MAC disease accounted for 78.2% of the patients in their 40s, including both men and women, and this increased with age, reaching 100% at age ≥80 years. Specifically, the percentage of patients with pulmonary *M. intracellulare* infection increased consistently with age, although this reflected an aging-associated increase among men. Second, BMI was <18.5 in approximately 40% of both men and women with pulmonary NTM disease, which was remarkably higher than the prevalence of underweight in the Japanese population. This trend was observed for all the causative mycobacterial species. Third, the percentage of male patients who were heavy smokers (BI ≥600) was relatively high for all mycobacterial species; 58.2% of total pulmonary NTM disease cases, 62.5% of those with pulmonary *M. avium* infection, 52.4% of those with pulmonary *M. intracellulare* infection, and 57.2% of those with pulmonary *M. kansasii* infection were heavy smokers. Fourth, systemic factors in pulmonary MAC disease were frequently observed in the order of malignant tumors (other than lung cancer), diabetes, rheumatoid arthritis, and tuberculosis. Further, local factors were observed in the order of BE, COPD, lung cancer, and bronchial asthma. In contrast, malignant tumors (other than lung cancer) and BE were not observed in those with pulmonary *M. kansasii* infection, although a relatively high percentage of patients had COPD (25%).

Considering the first observation of this study, the percentage of patients with pulmonary *M. intracellulare* infection increased consistently with age, although this reflected an aging-associated increase among men. These results suggest that aging may be a risk factor for disease onset, particularly in mycobacterial species. Regarding the difference between *M. avium* and *M. intracellulare*, the latter is known to be more pathogenic[8]. Moreover, a national epidemiological study showed that pulmonary *M. avium* infection is prevalent in East Japan whereas pulmonary *M. intracellulare* infection is prevalent in West Japan[2, 9]. To our knowledge, this study is the first to report an increased percentage of pulmonary *M. intracellulare* infection in aging men. Further studies are required to better understand the differences between the two mycobacterial species.

Concerning the second observation, regardless of the type of mycobacterial species, a low BMI may be a potential risk factor for disease onset in both men and women. However, we cannot exclude the possibility of patients with low BMI due to wasting as a result of chronic NTM infection. Further investigations are required to clarify this.

Regarding the third observation, smoking has been suggested as a risk factor for disease onset in pulmonary *M. kansasii* infection, although the percentage of heavy smokers was equal among male patients with either pulmonary MAC disease or *M. kansasii* infection in this study. The influence of smoking on the onset of pulmonary MAC disease requires further study.

Concerning the fourth observation, non-lung malignant tumors were observed in 17.8% of patients with pulmonary *M. avium* infection and 26.5% of those with pulmonary *M. intracellulare* infection. Malignant tumors, including lung cancer, were observed in 21.8% of those with pulmonary *M. avium* infection and 30.6% of pulmonary *M. intracellulare* infections. However, most cases of both non-lung and lung cancers were stages I to III and included many cases that had not undergone chemotherapy (data currently in submission). The relationship between malignant tumors and the onset of pulmonary MAC disease should be further analyzed. Interestingly, in France, England, the United States, and China, the percentages of patients with pulmonary NTM disease and non-lung malignant tumors were reported to be much lower at 11.8%, 12.7%, 17.7%, and 5.8%, respectively[10–13].

In general, BE is known to be frequently observed in patients with pulmonary NTM disease, but it was not observed in patients with pulmonary *M. kansasii* infection in this study; instead, COPD was more frequently observed (25%). Regarding the contribution of smoking to the onset of pulmonary *M. kansasii* infection, the smoking-induced damage may enable the colonization of the tracheal wall by *M. kansasii*, at least in part. In France, England, and the United States, the percentages of pulmonary NTM disease patients with COPD was reported to be higher, at 25.5%, 49.5%, and 28.8–35.0%, respectively[10–12, 14].

Our study has some limitations. First, the number of patients was small. However, they were a series of consecutive patients spanning 12 years, which is the main strength of this study. Second, this was a single-center study involving patients from one region of East Japan. Thus, there is a risk of bias in our observations, such as the prevalence of risk factors, and the results might not be generalizable to other regions of Japan or the country as a whole. Further studies are needed to confirm these results.

In conclusion, the prevalence of risk factors, which were previously reported in Western countries, is relatively high among Japanese patients with pulmonary NTM disease. In particular, the proportion of patients with low BMI and the proportion of heavy smokers was high among male patients,

regardless of the causative mycobacterial species. In contrast, the distribution of sex and age of onset differed according to the causative species, together with the prevalence of systemic and local factors. Additional examination of risk factors may help elucidate the mechanisms of disease onset.

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