Predictors of exacerbations of pulmonary MAC disease

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Abstract

Background and Objectives The number of patients with pulmonary *Mycobacterium avium* complex (MAC) disease is increasing worldwide, especially among middle-aged women and never-smokers. Although sex and smoking status have attracted attention as predictors of the development and exacerbation of pulmonary MAC disease, the exact associations remain unknown. The aim of the present study was to clarify the associations of sex and smoking status with the clinical characteristics of pulmonary MAC disease and to identify the predictors of exacerbations of pulmonary MAC disease.

Methods From April 2011 to May 2016, 128 MAC patients at our institute were newly diagnosed with pulmonary MAC disease according to the 2007 American Thoracic Society/Infectious Disease Society guideline. Their medical records were retrospectively examined for their clinical findings. The radiological findings at the time of the diagnosis and 1 year later were evaluated. Clinical characteristics were compared by smoking status and sex. To identify the natural predictors of exacerbation, multivariable analysis was performed with the data of 80 treatment-naïve patients. Results Female, never-smoker, and nodular/bronchiectatic (NB) type were common in patients with pulmonary MAC disease. Univariate analysis of data from treatment-naïve subjects showed that female, never-smoker, fewer lung diseases other than MAC, extensive radiological findings, and ≥ 3 lobes involved were significantly associated with exacerbations. On multivariate analysis, fewer lung diseases other than MAC, extensive radiological findings, and ≥ 3 lobes involved were significantly associated with exacerbations, but female and never-smoker were not. Conclusions In this study, the presence of extensive radiological findings, especially abnormal shadows in ≥ 3 lobes and absence of lung diseases other than MAC, rather than sex and smoking status, was a predictor of exacerbations of treatment-naïve pulmonary MAC disease.

Introduction

Epidemiologic data suggest that the incidence and prevalence of nontuberculous mycobacterium (NTM) infections are increasing in many countries.¹⁻⁶ *Mycobacterium avium* complex (MAC), including *M. avium* and *M. intracellulare*, is the most common aetiology in NTM.^{7,8} Although the progressive improvements in diagnostic technology such as chest computed tomography (CT) and genetic sequencing suggest that host and microorganism factors,⁹⁻¹² as well as environmental factors,¹² might be involved, the exact reason for the increasing prevalence of MAC remains unknown.

The clinical outcomes of pulmonary MAC disease vary widely. Some patients respond well to standard treatment including clarithromycin, ethambutol, and rifampicin, whereas others show resistance to standard treatment with poor outcomes, and some other patients remain stable without any treatment.^{7,13} Thus, it is critical to determine the predictors for the prognosis of patients with pulmonary MAC disease.

It has long been considered that the causative species are critical predictors, but the difference in the prognosis between *M. avium* and *M. intracellulare* infections still remains uncertain.^{14,15}

Sex and smoking status have also attracted attention as predictors of exacerbations of pulmonary MAC disease. The prevalence of pulmonary MAC disease is increasing particularly in never-smokers and middle-aged women.^{7,8,16} The effects of female hormones and adiponectin have been implicated,¹⁷ though the underlying mechanisms are yet to be determined.

The aim of the present study was to clarify the associations of sex and smoking status with the clinical characteristics of pulmonary MAC disease and to determine the significant predictors of exacerbations of pulmonary MAC disease.

Methods

Study population

From April 2011 to May 2016 at our institute, of the patients with suspected NTM, 315 NTM subjects were newly identified by cultures. Of them, 143 were diagnosed with NTM disease according to the 2007 American Thoracic Society/Infectious

Disease Society guideline.⁷ Those with a past history of NTM disease and NTM other than MAC were excluded from the present study. Finally, 128 subjects were enrolled in the present study (Figure 1). Clinical findings of the subjects including age, sex, past history of tuberculosis, laboratory data, and radiological findings were retrospectively examined from their medical records. To clarify the associations of sex and smoking status with the clinical characteristics of pulmonary MAC disease, the subjects were divided by sex and smoking status. To identify the significant predictors and to exclude treatment bias, analysis of only treatment-naïve subjects (patients who did not receive medications for MAC during the observation period) was also performed.

Microbiological examination

Acid-fast bacilli (AFB) were cultured in a Mycobacteria Growth Indicator Tube (MGIT) from extracted sputum or bronchial washings obtained by bronchoscopy. The sputum samples were obtained on two or more occasions after the initial presentation. The diagnosis of MAC was confirmed when cultures were positive for AFB, and the cultured AFB was subsequently confirmed as MAC by PCR. The diagnosis of pulmonary MAC disease was established when MAC was identified in sputum at least twice or in bronchial washings.

Radiological examination

According to a previous report,⁷ chest radiological findings were classified as fibrocavitary (FC) type or nodular/bronchiectatic (NB) type by high-resolution CT. Additionally, chest radiological findings at the time of initial diagnosis were scored as follows. The lung fields were divided into six zones based on anatomical structures, i.e. right upper, right middle, right lower, left upper, left lingular, and left lower. When any abnormal findings including cavities, bronchiectasis, small nodules, consolidations, atelectasis, and so on were found in each zone at the time of diagnosis, they were each counted as one point and summed up in the six zones (maximum 6 points). The subjects were further classified based on their clinical course during the follow-up period into three categories: exacerbation, no change, or improvement. Each category was defined as follows: exacerbation, abnormal shadows increased; no change, abnormal shadows remained stable on the whole; and improvement, abnormal shadows decreased. The three categories were classified by five respiratory specialists in a blinded fashion.

Patient management

When patients did not receive medications for MAC during the observation period, radiographic findings were evaluated at the time of the diagnosis and 1 year later. When patients received medications for MAC during the observation period, they all began standardized combination antibiotic therapy, which consisted of oral clarithromycin, rifampicin, and ethambutol.⁷ Radiographic findings were evaluated at the start of medications and 1 year later. Those who discontinued medications and received medications for less than 6 months were excluded in the analysis of the clinical response to medications.

Statistical analysis

The patients' characteristics are presented as means±standard deviation (SD). Numerical data are expressed as numbers (%). The differences between groups were examined for significance using the Mann-Whitney *U* test or Fisher's exact test, as appropriate. To determine factors related to pulmonary MAC disease in treatment-naïve patients, univariable and

multivariable Cox proportional hazard regression analyses were performed. All analyses were performed using SPSS Statistical software (version 22.0; IBM Japan, Tokyo, Japan). *P* values < 0.05 were considered significant.

Results

Baseline characteristics of pulmonary MAC patients

During the study period, 128 patients with pulmonary MAC disease were enrolled, and their baseline characteristics are summarized in Table 1. The causative organisms included *M. avium* in 100 patients (82.6%) and *M. intracellulare* in 21 patients (17.4%). Mixed infections (*M. avium* and *M. intracellulare*) were found in 7 patients. All patients were HIV-negative. Their average age was 75.1±12.8 years, and 80% of patients were over 65 years of age. Female (69.5%), never-smoker (61.7%), and NB type (78.9%) were predominant in MAC patients. The average BMI was slightly low (19.1 kg/m²). Medications for MAC were given to 39 (30.5%) patients during the observation period. The average number of abnormal lung zones was 3.27.

Comparison of pulmonary MAC patients' characteristics by smoking status

A total of 124 subjects, excluding 4 patients with unknown smoking histories, were enrolled to compare the characteristics by smoking status (Table 2). There were no significant differences in age and laboratory data irrespective of smoking status. Compared with current and past smokers, never-smokers had a significantly higher ratio of females, lower BMI, fewer lung diseases other than MAC disease (including chronic lung disease such as chronic obstructive lung disease, bronchial asthma, lung cancer, and so on), and more extensive radiological findings.

Comparison of pulmonary MAC patients' characteristics by sex

Compared to male patients, female patients had significantly lower BMI, serum CRP levels, and lung diseases other than mycobacterial diseases, and significantly fewer had a smoking history, while they had significantly higher serum albumin levels (Table 3). Clinical outcomes were comparable, but female patients received MAC therapy significantly more frequently than male subjects.

Comparison of female pulmonary MAC patients' characteristics by smoking status

Approximately two-thirds of male subjects had a smoking history, as shown in Table 3. The effects of smoking on the clinical characteristics of pulmonary MAC disease were evaluated only in female subjects (n=86) (Table 4). Compared to current and past smoker female patients, never-smoker female patients had significantly higher total protein, fewer lung diseases other than MAC, more extensive radiological findings, and a higher frequency of exacerbations at 1 year after diagnosis.

Predictors of exacerbation in treatment-naïve pulmonary MAC subjects

To exclude the bias of treatment because the treatment period was not fixed, univariate analysis was performed using only the data of treatment-naïve subjects (Table 5). The results indicated that female, never-smoker, fewer lung diseases other than MAC, more extensive radiological findings, and ≥3 lobes involved were significantly associated with exacerbations. Multivariate analysis was performed with items that showed significant differences on univariate analysis. On multivariate

analysis, fewer lung diseases other than MAC, more extensive radiological findings, and ≥ 3 lobes involved were significantly associated with exacerbations, whereas female sex and never-smoker were not found to be exacerbating factors.

Discussion

In the present study, *M. avium* was the predominant species, found in 82.6% of MAC patients. The rate of patients with *M. avium* infection was similar to other recent reports.¹⁸ Similarly, there were more female than male patients in the present study. Generally, pulmonary MAC diseases develop more frequently in female than in male patients. A recent biological study reported the role of estrogen in the development of pulmonary MAC disease, whereas the role of sex in disease susceptibility is yet to be determined.¹⁹

Smoking status might also be associated with the development of pulmonary MAC disease.²⁰ Smoking is a representative risk factor for human diseases, not only respiratory diseases, but also in general. Few diseases likely occur in never-smokers. For example, quitting smoking is a risk factor for hypersensitivity pneumonia²¹⁻²³ and sarcoidosis.²⁴ To determine the role of smoking status in the pathogenesis of pulmonary MAC disease, the present study compared patients' characteristics based on smoking status and found that never-smoker MAC patients had a significantly higher frequency of radiological exacerbations than current and past smokers. Nonetheless, it is impossible to conclude that never-smoking is a factor associated with exacerbations of pulmonary MAC disease, since many never-smoker MAC patients were female in the present study, and treatment status varied. Additionally, current and past smokers seemed to undergo radiological examinations more frequently than never-smokers, because they had a significantly higher frequency of other underlying lung diseases. Thus, there may be more opportunities to identify the early phase of pulmonary MAC disease in current and past smokers than in never-smokers.

To evaluate female sex as an exacerbating risk for pulmonary MAC disease, patients' characteristics were compared by sex. In treatment-naïve subjects, the frequency of radiological exacerbations was similar in both sexes. Although there was a significant difference in the frequency of MAC therapy between male and female patients, the responses to MAC therapy could not simply be compared by sex, though they seemed to be worse in women (7/7 of male and 16/32 of female patients improved following MAC therapy). The exact mechanisms of treatment resistance (cases that did not have improved radiological findings after 1 year despite MAC treatment for more than half a year) in female MAC patients remain unclear. In the present study, female patients had very low BMIs, and the role of poor nutritional status was suggested, whereas serum albumin levels were rather higher in female patients, so that nutritional status alone did not explain the mechanisms. Other factors including adiponectin and wet environmental exposure might be involved in treatment resistance.^{12,17}

In order to focus on smoking status and exclude sex as an exacerbating factor for MAC disease, patients' characteristics by smoking status were compared only in female patients. Never-smoker female patients had a significantly higher frequency of radiological exacerbations than current- and past-smoker female patients. This is probably due to significantly more radiological abnormalities at initial diagnosis in the never-smoker patients. Since never-smoker female patients had fewer other pulmonary diseases, diagnosis at the hospital was delayed, and as a result, they were likely discovered in an advanced state.

To determine the predictors of natural exacerbations, univariate logistic regression analysis was performed with the data of treatment-naïve patients, and it indicated that female sex, never-smoker, extensive abnormal shadows, ≥ 3 lobes with abnormal shadows, and the absence of other underlying lung diseases were significant. Multivariate logistic regression analysis demonstrated that the presence of more extensive radiological findings in untreated patients (a larger affected area) was associated with exacerbations based on the probabilities of reactivation or dissemination of the infection. Female sex and never-smoker were not associated with exacerbations, and the associations of sex and smoking status with the clinical outcomes of pulmonary MAC disease could not be clarified. Although some authors reported radiological scoring methods in pulmonary MAC disease,^{25,26} they were complicated and required much effort. Compared to these reports, the present scoring system had several limitations. It just counted the number of abnormal lesions irrespective of their volume and

characteristics. Nonetheless, it can be easily performed in actual clinical practice and can potentially predict the natural course of pulmonary MAC disease, as suggested by this report.

Conclusion

Women and never-smokers were predominant among patients with pulmonary MAC diseases. The most critical exacerbating factor of pulmonary MAC disease over 1 year is the presence of extensive abnormal shadows, especially the presence of abnormal shadows in ≥ 3 lobes in the lung. Thus, clinical attention should be focused on early diagnosis, since the presence of more extensive radiological findings in untreated patients (a larger affected area) was associated with exacerbations.

Abbreviations

ALB: serum albumin; CRP: serum C-reactive protein; CT: computed tomography; FC: fibrocavitary; MAC: *Mycobacterium avium* complex; NB: nodular/bronchiectatic; NTM: nontuberculous mycobacterium; TP: serum total protein

Declarations

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Availability of data and materials

The anonymised datasets analysed during the current study are available from the corresponding author on reasonable request.

Authors' contributions

N. K. collected data, analysed data, created the tables and figures, designed the study, and wrote and revised the manuscript. C. N., T. O., K. W., K. N., C. I., and H. M. collected data. H. M. critically revised the manuscript. All authors read and approved the final manuscript.

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Competing interests

All authors declare no conflicts of interest in relation to this article.

Consent for publication

Not required.

Ethics approval and consent to participate

This research was conducted using information previously collected in the course of normal care (without an intention to use it for research at the time of collection).

This study received ethical approval from the Special Committee of Toho University Ohashi Medical Center (project registration number H16053).

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Tables

Table 1. Baseline characteristics of pulmonary MAC patients (n=128)

Age, y	75.1±12.8
Sex (male/female)	39(30.5%)/89(69.5%)
Smoking history (current/past/never/unknown)	1(1%)/44(34.4%)/79(61.7%)/4(3.1%)
BMI (kg/m ²)	19.05±2.96
TP (g/dl)	7.29±0.77
ALB (g/dl)	3.70±0.61
CRP (mg/dl)	1.53±3.29
Previous tuberculosis, n (%)	13 (10.2%)
Lung disease other than mycobacterial disease, n (%)	52 (40.6%)
Smear/culture/BAL	29(22.7%)/64(50%)/35(27.3%)
Positive AFB smear, n (%)	29 (22.7%)
<i>M. avium</i> / <i>M. intracellulare</i> /avium+intracellulare	100(78.1%)/21(16.4%)/7(5.5%)
FC type/NB type	27 (21.1%) / 101 (78.9%)
MAC therapy during follow-up	39 (30.5%)
Zone of radiological findings (n.)	3.27±1.54

Data are presented as means±SD (standard deviation) or numbers (%).

AFB=acid-fast bacilli, ALB=serum albumin, CRP=serum C-reactive protein, FC=fibrocavitary, MAC=*Mycobacterium avium* complex, NB=nodular/bronchiectatic, TP=serum total protein

Table 2. Comparison of pulmonary MAC patients' characteristics by smoking status (n=124)

	Current and past smokers (n=45)	Never-smokers (n=79)	P-value
Age, y	75.0±13.9	75.6±12.0	0.76
Sex (male/female)	28 / 17 (62.2% / 37.8%)	10 / 69 (12.7% / 87.3%)	<0.001**
BMI (kg/m ²)	19.8±3.28	18.4±2.63	0.03*
TP (g/dl)	7.15±0.88	7.36±0.71	0.29
ALB (g/dl)	3.56±0.70	3.77±0.56	0.13
CRP (mg/dl)	2.10±4.42	1.25±2.51	0.16
Previous tuberculosis, n (%)	5 (11.1%)	8 (10.1%)	0.56
Lung disease other than mycobacterial disease, n (%)	28 (62.2%)	26 (32.9%)	0.001**
Positive MAC smear, n (%)	9 (17.8%)	20 (25.3%)	0.23
<i>M. avium</i> / <i>M. intracellulare</i> /avium+intracellulare	36 (80%) / 7 (15.6%) / 2 (4.4%)	62 (78.4%) / 13 (16.5%) / 4 (5.0%)	0.51
FC type/NB type	10 (22.2%) / 35 (77.8%)	17 (21.5%) / 62 (78.5%)	0.93
Zone of radiological findings, n (%)	2.76±1.45	3.58±1.52	0.003**
Improvement/no change/exacerbation/unknown	10(22.2%)/28(62.2%)/6(13.3%)/1(2.2%)	13(16.5%)/41(51.9%)/21(26.6%)/4(5%)	0.09
MAC therapy [‡]	13 (28.9%)	26 (32.9%)	0.40

‡: consisted of oral clarithromycin, rifampicin, and ethambutol over 6 months (MAC therapy). See footnote of Table 1 for expansions of abbreviations.

*: $P < 0.05$; **: $P < 0.01$

Table 3. Comparison of pulmonary MAC patients' characteristics by sex (n=128)

	Male (n=39)	Female (n=89)	<i>P</i> -value
Age, y	78.5±9.15	73.7±13.9	0.05
Smoking history (current/past/never/unknown)	0 / 28 (73.1%) / 10 (26.3%) / 1	1 / 16 (19.8%) / 69 (80.2%) / 3	<0.01*
BMI (kg/m ²)	20.3±2.84	18.5±2.84	<0.01*
TP (g/dl)	7.16±0.97	7.36±0.67	0.55
ALB (g/dl)	3.48±0.74	3.79±0.53	0.01*
CRP (mg/dl)	2.17±3.38	1.26±3.23	0.01*
Previous tuberculosis, n (%)	4 (10.3%)	9 (10.1%)	0.60
Lung disease other than mycobacterial disease, n (%)	24 (61.5%)	38 (42.7%)	0.04*
Positive MAC smear, n (%)	9 (23.1%)	20 (22.5%)	0.55
<i>M. avium</i> / <i>M. intracellulare</i> /avium+intracellulare	33 (84.6%) / 5 (12.8%) / 1 (2.6%)	67 (73.5%) / 16 (18.0%) / 6 (6.7%)	0.29
FC type/NB type	8 (20.5%) / 31 (79.5%)	19 (21.3%) / 70 (78.7%)	0.56
Zone of radiological findings (n)	3.08±1.58	3.36±1.52	0.46
Improvement/no change/exacerbation/unknown	8(20.5%)/23(59%)/6(15.4%)/2(5.1%)	16(18%)/47(52.8%)/21(23.6%)/5(5.6%)	0.23
MAC therapy [‡]	7 (17.9%)	32 (36.0%)	0.03*

See footnotes of Tables 1 and 2 for expansions of abbreviations.

Table 4. Comparison of pulmonary MAC female patients' characteristics by smoking status (n=86)

	Current and past smokers (n=17)	Never-smokers (n=69)	P-value
Age, y	68.7±18.3	75.3±12.2	0.21
BMI (kg/m ²)	18.7±3.75	18.3±2.64	0.84
TP (g/dl)	7.01±0.57	7.42±0.68	0.02*
ALB (g/dl)	3.80±0.60	3.80±0.53	0.85
CRP (mg/dl)	1.58±5.31	1.22±2.60	0.51
Previous tuberculosis, n (%)	2 (11.8%)	7 (10.1%)	0.56
Lung disease other than mycobacterial disease, n (%)	12 (70.6%)	26 (37.7%)	0.01*
Positive MAC smear, n (%)	3 (17.6%)	17 (24.6%)	0.40
<i>M. avium</i> / <i>M.</i> <i>intracellulare</i> /avium+intracellulare	14 (82.6%) / 2 (11.8%) / 1 (5.9%)	51 (73.9%) / 13 (18.8%) / 3 (4.3%)	0.43
FC type/NB type	4 (23.5%) / 13 (76.5%)	14 (20.3%) / 55 (79.7%)	0.49
Zone of radiological findings, n (%)	2.41±1.28	3.54±1.48	0.006**
Improvement/no change/exacerbation/unknown	6(35.3%)/10(58.8%)/1(5.9%)/0	10(14.5%)/36(52.2%)/18(26.1%)/5(7.2%)	0.04*
MAC therapy [‡]	8 (47.1%)	20 (29.0%)	0.13

See footnotes of Tables 1 and 2 for expansions of abbreviations.

Table 5. Predictors of exacerbation in treatment-naïve pulmonary MAC subjects (n=80)

	Univariate analysis		Multivariate analysis	
	HR (95%CI)	P-value	HR (95%CI)	P-value
Age, y	0.963 (0.922-1.005)	0.085		
Sex (Female)	3.116 (1.022-9.498)	0.046*		
Never-smoker	3.900 (1.283-11.85)	0.016*		
BMI (kg/m ²)	0.990 (0.839-1.168)	0.904		
TP (g/dl)	1.702 (0.922-3.140)	0.089		
ALB (g/dl)	1.920 (0.863-4.274)	0.110		
CRP (mg/dl)	0.944 (0.797-1.118)	0.503		
Previous tuberculosis, n (%)	1.905 (0.523-6.939)	0.329		
Lung disease other than mycobacterial disease, n (%)	0.287 (0.108-0.767)	0.013*	0.306 (0.109-0.856)	0.024*
Positive MAC smear, n (%)	2.222 (0.741-6.663)	0.154		
<i>M. intracellulare</i>	0.889 (0.240-3.297)	0.860		
FC type	1.190 (0.355-3.991)	0.085		
Zone of radiological findings, n (%)	1.587 (1.133-2.222)	0.007**	1.565 (1.103-2.221)	0.012*
Involved lobes ≥3	4.523 (1.488-13.75)	0.008**	4.349 (1.385-13.65)	0.012*
Involved lobes ≥2	4.252 (0.962-18.79)	0.056		

Figures

Figure 1

Flow chart of patients diagnosed with pulmonary MAC disease between April 2011 and May 2016. MGIT=mycobacterial growth indicator tube NTM=nontuberculous mycobacterium MAC=Mycobacterium avium complex