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Original Article

The characteristics of patients with pulmonary *Mycobacterium avium-intracellulare* complex disease diagnosed by bronchial lavage culture compared to those diagnosed by sputum culture

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ABSTRACT

Background and objective: The utility of bronchoscopy for the diagnosis of pulmonary *Mycobacterium avium-intracellulare* complex (MAC) disease has been reported; however, which patients require bronchoscopy remains unclear. Our objective was to identify the characteristics of the patients in whom bronchoscopy is needed for the diagnosis of MAC disease.

Methods: Fifty-four patients with pulmonary MAC disease were divided into two groups according to established diagnostic criteria: 39 patients were diagnosed by sputum culture and 15 patients were diagnosed by bronchial lavage culture. We analysed the differences in demographic and clinical characteristics as well as microbiological and radiological data between the two groups.

Results: There were no significant differences in age, sex, smoking status, MAC species, underlying diseases, or steroid use. Significantly more patients diagnosed by sputum culture than bronchial lavage culture had a positive sputum smear for acid-fast bacilli (79.5% vs. 0.0%, respectively; $p < 0.001$) and any symptoms (75.3% vs. 46.2%, respectively; $p = 0.0059$). No significant differences were found in the prevalence of each computed tomography finding, including nodules, air-space disease, bronchiectasis, and cavities. However, more patients diagnosed by sputum culture than bronchial lavage culture had abnormalities in the left upper division (48.7% vs. 13.3%, respectively; $p = 0.017$) and higher numbers of affected lobes (4.3 ± 1.4 vs. 3.3 ± 1.6, respectively; $p = 0.034$).

Conclusion: If patients suspected of having pulmonary MAC disease have a negative sputum smear, no symptoms, no abnormal findings in the left upper division, or fewer affected lobes on computed tomography, bronchoscopy might be needed for the diagnosis.

1. Introduction

The prevalence of pulmonary nontuberculous mycobacterial (NTM) disease continues to increase worldwide, particularly in developed countries [1]. A recent study showed that the national prevalence of pulmonary NTM disease in Japan in 2005 was 33–65 per 100,000 population-years and that *Mycobacterium avium-intracellulare* complex (MAC) was the most common pathogen involved in pulmonary NTM disease [2].

Pulmonary MAC disease in immunocompetent patients is generally indolent or slowly progressive, but it can result in extensive lung destruction and respiratory failure in some cases. In two studies in Japan, Hayashi and Ito estimated that the 5-year mortality rate associated with pulmonary MAC disease was 5.4% and 5.1%, respectively [3,4]. In addition, patients often develop various symptoms such as chronic or recurrent cough, sputum production, fatigue, malaise, dyspnoea, fever, hemoptysis, chest pain, and weight loss [5]. Two typical radiological abnormalities of pulmonary MAC disease have been described: the fibrocavitary type, which is characterized by development in middle-aged male smokers and the presence of apical fibrocavitary lesions, and the

Abbreviations: NTM, nontuberculous mycobacterial; MAC, *Mycobacterium avium-intracellulare* complex; AFB, acid fast bacilli; CT, computed tomography; IgA, immunoglobulin A.

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nodular bronchiectatic type, which is characterized by development in post-menopausal, never-smoking female patients and the presence of small nodules and bronchiectasis involving the right middle lobe or lingua. The fibrocavitary type is generally progressive; therefore, immediate treatment initiation is recommended. In contrast, the nodular bronchiectatic type tends to show slower progression, and long-term follow-up is recommended until clinical or radiographic progression occurs [5]. However, even in patients with the nodular bronchiectatic type, death may be related to disease progression [5]. Lee and Hwang reported that 47.5% and 64.7% of untreated patients with the nodular bronchiectatic form of MAC disease had developed disease progression and required treatment within 32 ± 21 months and 3 years, respectively [6,7]. Additionally, we cannot definitively distinguish between these two types of disease in some patients; 7.3% and 9.0% of patients with pulmonary MAC disease could not be definitively classified in two previous studies [3,7]. Therefore, to avoid missing the optimal timing of treatment initiation, early diagnosis of pulmonary MAC disease and exclusion of other pulmonary diseases including tuberculosis is important.

According to the 2007 American Thoracic Society guidelines for the diagnosis of NTM infection, the diagnosis of pulmonary NTM disease requires the patient to meet clinical and microbiologic criteria including either (1) positive culture results from at least two separate expectorated sputum samples, (2) positive culture results from at least one bronchial wash or lavage, (3) transbronchial or other lung biopsy with mycobacterial histopathologic features (granulomatous inflammation or acid-fast bacilli [AFB]), and positive culture for NTM species or (4) biopsy showing mycobacterial histopathologic features (granulomatous inflammation or AFB) and one or more sputum or bronchial washings that are culture-positive for NTM species [5]. The effectiveness of bronchial lavage or biopsy via a bronchoscope for the diagnosis of pulmonary MAC disease has been reported in some previous studies [8–13]. However, no studies have assessed which patients require bronchoscopy for the diagnosis of pulmonary MAC disease. Bronchoscopy is generally safe, but complication rates associated with fibre optic bronchoscopy reportedly range from <0.1% to 11.0%, with mortality rates generally reported from 0.0% to 0.1% [14]. In addition, patients often experience various discomforts during bronchoscopy; therefore, it should be avoided if possible.

In this study, we assessed the differences in demographic and clinical characteristics as well as microbiological and radiological data between patients diagnosed with pulmonary MAC disease by sputum culture and those diagnosed by bronchoscopy. The aim of the study was to identify the characteristics of patients in whom bronchoscopy is needed for the diagnosis of MAC disease.

2. Patients and methods

2.1. Study populations

Fifty-eight patients with pulmonary MAC disease fulfilling the American Thoracic Society guidelines for the diagnosis of NTM infection [5] who visited Ijinkai Takeda General Hospital from April 2014 to September 2016 were eligible. Among them, one patient with a complicating infection by *Mycobacterium abscessus* was excluded. Additionally, one patient with missing data on computed tomography (CT) findings at diagnosis and two patients whose CT findings of pulmonary MAC disease could not be assessed because of coexisting disease (one had rheumatoid lung disease and the other interstitial lung disease) were excluded. Finally, 54 (93.1%) patients were included in the study. Thirty-nine (72.2%) of these patients were diagnosed with pulmonary MAC disease by two or more positive sputum cultures. Bronchial lavage was performed in the remaining 15 patients who were suspected of having pulmonary MAC disease based on chest X-ray or CT findings but in whom a diagnosis could not be obtained because of negative cultures from at least 3 consecutive sputum samples or the absence of sputum expectoration. We wedged the segmental or subsegmental bronchus with abnormal lesions on chest CT, injected 20 ml of sterile normal saline, and aspirated the lavage fluid via a bronchoscope. We were able to diagnose pulmonary MAC disease in all 15 patients with one positive bronchial lavage culture. Whether transbronchial lung biopsy should be performed was decided by each primary physician. No patients were diagnosed by surgical lung biopsy. No patients had obvious risk factors for human immunodeficiency virus infection. The ethics review board of Ijinkai Takeda General Hospital approved the study protocol (T031), and written informed consent was obtained from each patient.

2.2. Date collection and data analysis

We retrospectively reviewed the clinical records of the patients and collected data on symptoms (e.g., cough, sputum or bloody sputum), underlying diseases, smoking status, sputum smear and culture results, and chest CT findings. All of these data were obtained at the time of diagnosis of pulmonary MAC disease. The day of diagnosis was defined as either the day on which expectorated sputum provided the second positive culture result for MAC or the day on which bronchial lavage was performed.

We also reviewed the patients' CT findings, including the prevalence of nodules, air-space disease, bronchiectasis, cavities, which lung lobes had parenchymal abnormalities, and the number of involved lobes. We considered that a lung comprised six lobes; the lingual division of the left upper lobe was considered a separate lobe. Evaluation of the CT findings was performed by two pulmonary clinicians.

We analysed the differences in demographic and clinical characteristics and microbiological and radiological data between the patients diagnosed by sputum culture and those diagnosed by bronchial lavage culture. Associations of each categorical and continuous variable between the cases and controls were tested by the chi-square or Wilcoxon test, respectively. A software package (JMP, version 6.0.3, SAS Institute, Cary, NC) was used for statistical analysis. A p-value of <0.05 was considered statistically significant.

3. Results

3.1. Patient characteristics

Fifty-four patients with a mean age of 71.3 ± 8.9 years (range, 44–87 years) were enrolled in the study. Females and nonsmokers comprised the majority of the patients (75.9% and 66.7%, respectively).

The patients were divided into 2 groups according to the diagnostic criteria: 39 patients were diagnosed by sputum culture (mean age, 71.6 ± 9.6 years; 74.4% females), and 15 patients were diagnosed by bronchial lavage culture (mean age, 70.6 ± 6.7 years; 80.0% females). The characteristics of the study patients are shown in Table 1. No significant differences were found in age, sex, or smoking status between the two groups. *Mycobacterium avium* tended to be more prevalent in both patients diagnosed by sputum and those diagnosed by bronchial lavage culture (69.2% and 53.3%, respectively). There were no significant differences in MAC species, underlying diseases, or steroid use (dexamethasone at 0.5 mg/day was prescribed for adrenal insufficiency in one patient diagnosed by sputum culture).

Nine (60.0%) of 15 patients diagnosed by bronchial lavage could not expectorate sputum. While 31 (79.5%) of 39 patients diagnosed