



## Characteristics of pulmonary *Mycobacterium avium* complex disease diagnosed later in follow-up after negative mycobacterial study including bronchoscopy



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### ABSTRACT

**Background:** We occasionally experience cases suspected of pulmonary *Mycobacterium avium* complex (MAC) disease without positive bacterial cultures.

**Objective:** To evaluate features of pulmonary MAC cases diagnosed later in the follow-up after negative intensive investigation.

**Methods:** We defined and compared three groups; the first study negative (FSN) group, the first study positive (FSP) group, and MAC negative group. The FSN group consisted of patients negative for MAC isolation by bronchial washing performed between 2007 and 2011, but positive later. Patients with positive MAC cultures in the first study were incorporated into the FSP group. MAC negative group consisted of MAC suspects without MAC isolation in the follow-up.

**Results:** Twenty-four patients were classified as FSN group, 61 as MAC negative group and 265 as FSP group. FSN group exhibited more solitary nodule pattern ( $n = 7$  in FSN,  $n = 6$  in FSP;  $p < 0.001$ ) and less nodular/bronchiectatic (NB) diseases ( $n = 17$  in FSN,  $n = 245$  in FSP;  $p < 0.001$ ). When limited to NB type, the FSP group had more cavitations (6% in FSN, 32% in FSP;  $p = 0.028$ ). Patients with more than three lung lobes involved were more frequent in the FSN group compared with FSP group with negative sputum cultures (65% vs 34%;  $p = 0.014$ ) and with MAC negative group (65% vs 28%;  $p = 0.009$ ).

**Conclusions:** Patients diagnosed as pulmonary MAC disease in the follow-up duration tend to show solitary nodular pattern or NB pattern without cavitation. In FSN patients with NB pattern, more lung lobes were involved in the first study, suggesting subsequent MAC infection onto the underlying ectatic bronchi.

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## 1. Introduction

*Mycobacterium avium* complex (MAC), comprised of *M. avium* and *Mycobacterium intracellulare*, is the most common isolated strain in the infectious diseases caused by nontuberculous

mycobacteria (NTM) worldwide [1]. The diagnosis was confirmed by isolation of the pathogen multiple times from sputum or other respiratory specimens. More invasive procedures such as bronchial washing and CT-guided needle aspiration for the suspected lesions would be needed when sputum cultures revealed negative or were unavailable [1–3].

We occasionally experience patients exhibiting positive conversion of MAC cultures from respiratory specimen later in the follow-up although their preceding close examinations including bronchial washings revealed negative for MAC. Negative MAC isolation in the first study allowed two possible interpretations; false negative results in cases of true MAC infection or secondary MAC infection in cases of no MAC infection. It would be valuable to elucidate the factors contributing the first study results, especially

**Abbreviations:** MAC, *Mycobacterium avium* complex; NTM, nontuberculous mycobacteria; ATS, American Thoracic Society; IDSA, Infectious Disease Society of America; FSN, first study negative; FSP, first study positive; NB, nodular/bronchiectatic; FC, fibrocavitary; CF, cystic fibrosis; CRP, C-reactive protein; TBLB, transbronchial lung biopsy; BMI, body mass index.

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for estimating the necessity to treat as a MAC pulmonary infection and for evaluating the risk of introducing immunosuppressive therapies to rheumatic diseases [4,5]. In this study, we retrospectively analyzed patients with MAC pulmonary diseases diagnosed later in the follow-up period after negative intensive examinations and discussed whether latent or secondary MAC infection was dominant in such cases.

## 2. Methods

### 2.1. Patients

To elicit pulmonary MAC disease cases diagnosed later in the follow-up after negative bronchial washing fluid culture results, we selected patients using database for bronchial washing culture performed from January 2007 through December 2012 at Tokyo National Hospital, and checked whether they were diagnosed as pulmonary MAC by December 2013 (Fig. 1). Diagnosis of pulmonary MAC disease was made when the patients fulfilled the 2007 American Thoracic Society/Infectious Disease Society of America (ATS/IDSA) criteria for MAC lung disease [1] or their resected lung specimen showed mycobacterial histopathological features and positive culture/PCR results for MAC. We excluded those who had been diagnosed as MAC lung disease before January 2007 and whose chest CT was not available. We defined elicited MAC disease patients as mentioned above as first study negative (FSN) group.

In order to clarify the characteristics of FSN group, we compared their data with that of cases which we called as first study positive (FSP) group that consisted of patients who had met 2007 ATS/IDSA criteria by sputum culture or bronchial washing fluid culture performed within 3 months after their first visit to our hospital between January 2007 through December 2012 (Fig. 1). In addition, we also reviewed MAC suspects whose respiratory specimens remained negative for MAC isolation and called them as “MAC negative group” in this study. This group patients were defined as those who underwent bronchial washing cultures between 2007 and 2012 because of suspicion of MAC diseases initially and were

followed up without evident MAC isolation until 2013 (Fig. 1). Patients who were diagnosed as MAC disease prior to the adopted duration or who did not have chest CT image were excluded as in FSN group (Fig. 1).

### 2.2. Design

This was a retrospective cohort study. We reviewed medical records and checked clinical information including age, sex, smoking history, symptoms, comorbidities, and prescription including immunosuppressive drugs and macrolides in both groups. Chest CT scans performed within 1 month after the first visit were checked and their findings were categorized into 5 groups; nodular/bronchiectatic (NB) disease, fibrocavitary (FC) disease, solitary nodule, disseminated disease and hypersensitivity-like disease [1]. If patients' radiological abnormalities did not fit these 5 subtypes but were considered as manifestation caused by MAC infection based on microbiological examination, such cases were categorized as “Others”. Microbiological test results from respiratory specimens and laboratory test results including serum albumin, white blood cell count and CRP were also evaluated. To assess the characteristics of FSN group, we compared clinical, laboratory, microbiological and radiological findings of them with those of FSP group and with MAC negative group.

In FSN group, specimens in which MAC was isolated were checked as well as durations needed to reveal MAC infections after bronchial washing that had been performed as the first study.

### 2.3. Statistical analysis

Data are shown as number of patients with percentage. Age is shown as median with range, and blood sample test results is done as average  $\pm$  SD. Chi-squared test or Fisher's exact test, and Mann Whitney U test were used to compare patients' characteristics between the FSN and FSP groups, or between FSN group and MAC suspects whose microbiological examinations remained negative for MAC.  $P < 0.05$  was considered as statistically significant.

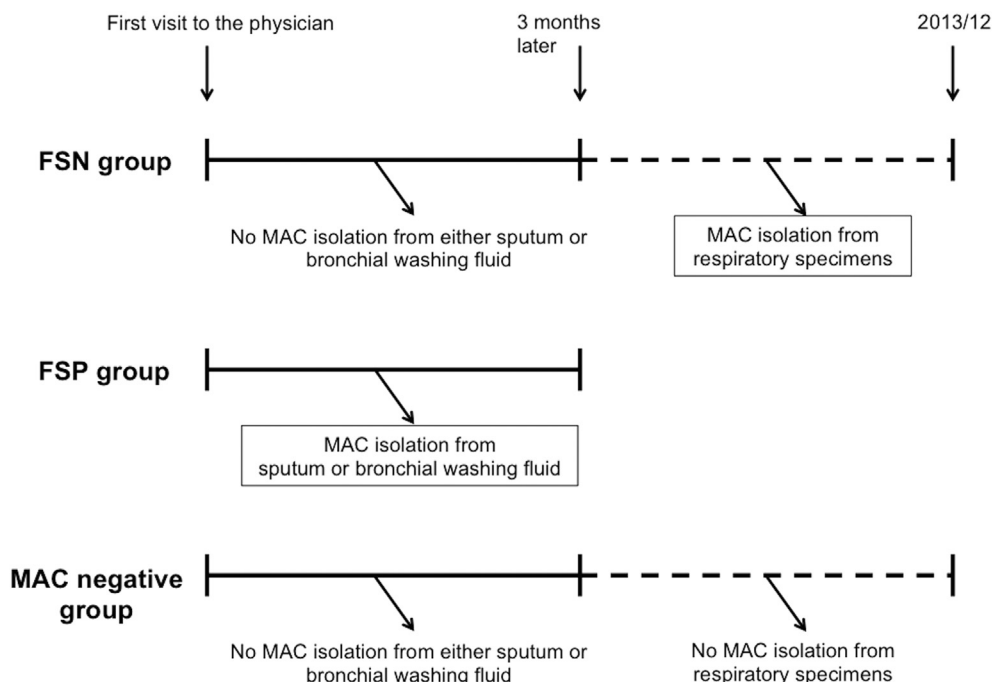


Fig. 1. The definition of the FSN group, FSP group and MAC negative group. FSP: first study positive, FSN: first study negative.

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