

## SHORT COMMUNICATION

**Chronic necrotizing pulmonary aspergillosis as a complication of pulmonary *Mycobacterium avium* complex disease**

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**Objective and background:** To investigate the characteristic clinical features of chronic necrotizing pulmonary aspergillosis (CNPA) as a complication of pulmonary *Mycobacterium avium* complex (MAC) disease.

**Methods:** Clinical analysis of nine cases without a history of old pulmonary tuberculosis in whom CNPA was found to be a complication during the follow-up period for MAC disease.

**Results:** The average duration from the diagnosis of pulmonary MAC disease to the diagnosis of CNPA was 36.0 months. Five patients received antituberculous therapy including clarithromycin for pulmonary MAC disease, but this treatment was ineffective in most. A positive culture for *Aspergillus* spp. from sputum and a bronchoscopic specimen and clinical evidence of a chronic infective process were recognized in all cases at the time of detection of CNPA. Serological fungal examinations for anti-*Aspergillus* IgG antibody were initially negative and became positive in all cases during the follow-up period of pulmonary MAC disease. The presence of CNPA surrounding the cavity previously caused by MAC was characterized by local thickening of the cavity with a fungus ball and the appearance of an infiltration shadow surrounding the cavity. In most of the cases, CNPA was at first treated with oral itraconazole and then with i.v. infusion of micafungin, but the clinical efficacy was generally poor.

**Conclusion:** The results of this study showed that during the long follow-up period of patients with pulmonary MAC disease it is important to not only carry out serological examinations, but also perform radiological examinations using chest CT.

**Key words:** chronic necrotizing pulmonary aspergillosis, pulmonary *Mycobacterium avium* complex disease, radiological examination, serological fungal examination.

**INTRODUCTION**

Chronic necrotizing pulmonary aspergillosis (CNPA) has been diagnosed in patients with diabetes mellitus, chronic renal failure, or collagen vascular disease as an underlying disease.<sup>1</sup> There has been only one case report regarding CNPA in which a cavity was

formed by pulmonary *Mycobacterium avium* complex (MAC) disease without a history of old pulmonary tuberculosis and this was experienced in our hospital.<sup>2</sup> Recently, the frequency of non-tuberculous mycobacteria has been increasing, and CNPA as a complication of pulmonary MAC disease seems to be increasing. The purpose of the present study was to prospectively evaluate the characteristic clinical features of pulmonary MAC disease complicated by CNPA without a history of old pulmonary tuberculosis.

**PATIENTS AND METHODS**

Patients in whom CNPA, without a history of old pulmonary tuberculosis was found to be a complication

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during the follow-up period for MAC disease and who were diagnosed at Kawasaki Medical School Hospital (1072 beds) or Asahigaoka Hospital (90 beds) between April 1994 and March 2004 were selected. The diagnostic criteria for non-tuberculous mycobacterial infection proposed by the American Thoracic Society (ATS) were satisfied,<sup>3</sup> and CNPA was diagnosed based on a positive culture of *Aspergillus* spp. from a sputum specimen or bronchoscopic specimen, clinical evidence of a chronic infective process (fever, weight loss, cough, high inflammatory markers), a positive reaction to *Aspergillus*-specific IgG antibody testing (Ochterlony's test)<sup>4</sup> and a characteristic progressive radiological abnormality such as an expanding thick-walled cavity.<sup>1</sup> Patients who had a history of old pulmonary tuberculosis or who were suspected of having had pulmonary tuberculosis based on radiological findings on past CXR before the diagnosis of pulmonary MAC disease were excluded from this study.

Clinical features were analysed with regard to background (age, gender, smoking history, alcohol intake and underlying diseases including pulmonary tuberculosis), clinical symptoms, laboratory data such as inflammatory markers and the duration from the diagnosis of pulmonary MAC disease to that of CNPA. We collected the following data: laboratory results of serum antifungal (*aspergillus* antigen and antibody) and microbiological examinations (culture, examination of sputum or bronchoscopic specimens); radiological findings using chest CT, presence of so-called fungus ball formation and any infiltration surrounding the cavity, and treatment efficacy and outcome for pulmonary MAC disease and CNPA. Chest CT was used to assess the thickness of the cavity wall caused by *aspergillus* infection, which was measured at the maximal width of the cavity wall and compared with that at the time of the initial diagnosis of pulmonary MAC disease. The clinical efficacy of treatment for pulmonary MAC disease was evaluated on the basis of the sputum conversion and sputum relapse rates, and clinical improvement was based on the radiological findings and the opinions of the attending respiratory specialists from an assessment undertaken as in previous studies.<sup>5-7</sup> The clinical efficacy of the treatment for CNPA was evaluated on the basis of improvement in clinical symptoms and a decrease in abnormal chest shadows.

## RESULTS

Nine patients complicated by CNPA were selected from among the 146 HIV-negative patients with pulmonary MAC disease who satisfied the ATS guideline criteria. The characteristics of the nine patients are shown in Tables 1 and 2. All the patients were Japanese with a median age of 70 years (66–77 years). The ratio of men to women was 4:5. Two patients were current smokers, two were ex-smokers and four drank alcohol regularly. Six patients had other underlying diseases in addition to pulmonary MAC diseases. Of these patients, four had diabetes mellitus with poor control of HbA<sub>1c</sub>, three had gastrointestinal diseases (gastric ulcer two, gastric cancer post operation one)

**Table 1** Patient characteristics (1)

Age (years, median)	62–77 (70)
Gender (male/female)	4:5
Smoking history	4
Alcoholic abuse history	4
Other underlying disease (with repetition)	6
Diabetes mellitus	4
Gastrointestinal disease (gastric ulcer 2, gastric cancer post operation 1)	3
Cardiovascular disease (angina pectoris 1)	1
Duration from NTM isolation to CNPA (months, mean ± SD)	18–72 (36.0 ± 19.6)
Causative microorganism of NTM	
<i>Mycobacterium avium</i>	5
<i>Mycobacterium intracellulare</i>	4
Treatment for NTM	5
(+) RFP + EB + SM + CAM	4
CAM	1
(-)	

CAM, clarithromycin; CNPA, chronic necrotizing pulmonary aspergillosis; EB, ethambutol; NTM, non-tuberculous mycobacterial disease; RFP, rifampicin; SM, streptomycin.

**Table 2** Patient characteristics (2)

Serological fungal examination	
Anti- <i>Aspergillus</i> antibody	9
Anti- <i>Aspergillus</i> antigen	2
β-D-glucan	7
Isolated <i>Aspergillus</i> spp.	
<i>Aspergillus fumigatus</i> (sputum 3, bronchoscopic specimens 5)	8
<i>Aspergillus niger</i> (sputum 1)	1
Treatment	
ITCZ p.o.	9
MCFG d.i.v.	4
AMPH intratracheal instillation	2
AMPH inhalation	2
Clinical effect	
Good	2
Poor	7

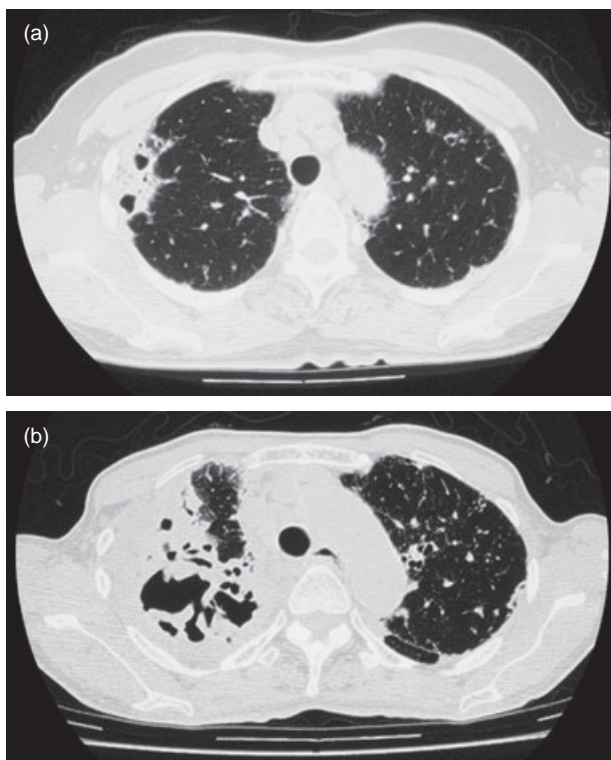
AMPH, amphotericin B; ITCZ, itraconazole; MCFG, micafungin.

and one had cardiovascular disease. The average duration from the diagnosis of pulmonary MAC disease to the diagnosis of CNPA was 36.0 ± 19.6 months (18–72 months). Clinical evidence of a chronic infective process such as weight loss (>5 kg within 3 months), fever (>38°C), and/or an increase of inflammatory markers was noted in all of the patients. Clinical symptoms such as haemoptysis or haemosputum, which was suggested CNPA, were recognized in six patients.

The causative non-tuberculous mycobacteria were *M. avium* in five patients and *Mycobacterium intrac-*

*ellulare* in four. With respect to the treatment for MAC disease, antituberculous therapy including clarithromycin was given in five patients. Although in four of these, it was used in combination with rifampicin, ethambutol, streptomycin and clarithromycin according to the ATS guidelines, in all cases the clinical efficacy was poor and the isolation of MAC continued. Serological fungal examinations were useful for the diagnosis of pulmonary aspergilloma. Anti-*Aspergillus* IgG antibody testing was positive in all cases, and  $\beta$ -D-glucan was positive in seven. However, aspergillus antigen testing was positive in only two. In eight patients, *Aspergillus fumigatus* was isolated from sputum specimens in three and bronchoscopic specimens in five, and *Aspergillus niger* was isolated from a sputum specimen in one case.

Radiologically, calcification was not seen in any of the patients, but local thickening of the cavity wall (over 25 mm at the maximal length of the cavity wall) and a so-called fungus ball were observed when compared with the cavity at the time of initial diagnosis of pulmonary MAC disease. Chest CT findings that were indicative of a mature aspergilloma, such as a fungus ball-like shadow and new infiltration shadows surrounding the cavity wall indicative of CNPA, were seen in all patients (Fig. 1).



**Figure 1** (a) Chest CT taken in December 1998 showing an infiltration shadow with two cavities (1 × 1 cm in size) in the right upper lobe (Case 1). (b) Chest CT taken in October 2003 showing a growing cavity with a fungus ball-like shadow (10 × 8 cm in size), and an infiltration shadow around the cavity in the right upper lobe.

All of the patients with CNPA were treated with itraconazole (ITCZ). Four then received an i.v. infusion of micafungin (MCFG). However, the clinical efficacy was good in only one. Specifically, although conversion of *Aspergillus* spp. in the specimens was achieved, all of the patients continued to be positive for the anti-*Aspergillus* IgG antibody and chest CT findings were unchanged or worsened. In four cases in which ITCZ oral administration or i.v. MCFG therapy was ineffective, amphotericin B was given by endobronchial instillation or inhalation. However, the clinical efficacy was good in only one.

## DISCUSSION

The radiological findings of pulmonary MAC disease without HIV infection have been classified into two groups: (i) one group resembling pulmonary tuberculosis, in which the characteristic findings are cavity formation and a micronodular shadow with a satellite lesion in segment 1 or 2 of the upper lobe; and (ii) the other group, primarily composed of middle-aged women with micronodular and transbronchial lesions, in which the characteristic findings are an aggregation of subpleural micronodules and thickening or dilatation of the bronchus in the middle and lingular lobes, although a few nodules can have cavities.<sup>8</sup> The nine cases in this study were categorized as belonging to the group resembling pulmonary tuberculosis. In these patients, the cavity that had been formed by pulmonary MAC disease over several years time increased transiently because CNPA was forming in and surrounding the cavity. CNPA was first proposed as an entity by Binder *et al.*<sup>9</sup> Since then, CNPA has been described as an infection that begins as an area of consolidation and which is associated with the development of adjacent pleural thickening. According to several reports, progressive cavitation generally develops after several months with or without the development of an intracavitary mycetoma.<sup>10,11</sup> Because all of the cases in this study were assessed every 6 months by chest CT during the 10 years follow-up period for pulmonary MAC disease, a comparatively early diagnosis of CNPA was obtained. In all patients, there was a chronic infective process, a positive culture of *Aspergillus* spp., a positive response on serological fungal examination and radiographical images showing new infiltrates surrounding the cavity wall, which are all indicative of CNPA. Therefore, the clinical diagnosis was assumed to be CNPA as a complication of pulmonary MAC disease. However, the possibility that the clinical manifestations might be due to pulmonary MAC disease rather than CNPA could not be completely excluded as the treatment response of patients with pulmonary MAC disease was very poor (all patients were smear-positive).

Chronic forms of pulmonary aspergillosis containing CNPA are the most frequent sequelae (25–75%) of pulmonary tuberculosis and have been observed in pre-existing intrapulmonary cavities, such as pulmonary cysts or ecstatic bronchi.<sup>8,12,13</sup> There have been no reports describing the clinical characteristics of CNPA with a fungus ball-like shadow in a cavity

definitely formed by pulmonary MAC disease, although there have been a few reports of superinfection by *Aspergillus* spp. of pulmonary lesions caused by *Mycobacterium xenopi*.<sup>14,15</sup> However, the frequency of non-tuberculous mycobacteria (MAC, etc.) has recently been increasing among patients in industrialized countries.<sup>16</sup> Many previously reported cases in which the underlying disease was pulmonary non-tuberculous mycobacterial disease may actually have been pulmonary tuberculosis complicated by the presence of chronic forms of pulmonary aspergillosis containing CNPA in a cavity.

With respect to the clinical diagnosis, in addition to the radiological findings, three types of laboratory examinations should be performed. Mycological examination of sputum or bronchoscopic specimens should be performed, as the positive rate of mycotic cultures from sputum has been commonly reported to range from 50% to 70%.<sup>1</sup> Careful attention must be paid to the treatment of these specimens because *Aspergillus* spp. may be ubiquitously present and contamination of a specimen can result in a false positive reaction. A positive serological reaction to anti-*Aspergillus* antibody (IgG) using Ochterlony's test<sup>3</sup> was useful for detecting chronic forms of pulmonary aspergillosis containing CNPA during follow up for pulmonary MAC disease. In all our cases, the previously negative serological reaction to anti-*Aspergillus* antibody became positive at the same time as the radiological finding of a local thickening of the cavity wall was made on chest CT. In immunocompetent patients on serological examination, the anti-*Aspergillus* antibody has been detected in more than 95% of cases with chronic forms of pulmonary aspergillosis.<sup>4,13</sup> Recently, PCR has been found to be useful for diagnosing CNPA by detecting serum aspergillus-specific genes.<sup>17</sup>

There is no overwhelmingly effective therapy for pulmonary MAC disease<sup>5-7</sup> and in all our patients, the underlying course of their MAC has been one of slow progression and the development of cavity lesions and MAC isolation. There have been no previous reports of the coexistence of MAC and *Aspergillus* spp. in the same cavity. For CNPA, the recommended treatment method is surgical resection of the cavitory lesion. However, conservative therapy, such as anti-fungal chemotherapy, was given to most patients with CNPA as many had pleural adhesions or decreased respiratory function. In the present study, a poor clinical result (efficacy: 22%) was observed in all cases receiving i.v. MCFG or oral ITCZ. Recently, new anti-fungal agents, including azole and echinocandin anti-fungal agents<sup>18,19</sup> have been developed that possess high antifungal activity against *Aspergillus* spp. However, the clinical efficacy of any of these agents against CNPA is expected to be low because the transition rate of antifungal agents into the cavity is poor.

This study reports the treatment of nine patients diagnosed as having CNPA in and surrounding a cavity formed by pulmonary MAC disease. The findings of this study indicate that it is necessary to be aware that pulmonary non-tuberculous mycobacterial disease has become one of the underlying pulmonary diseases that can be complicated by chronic forms of

pulmonary aspergillosis containing CNPA. To detect the CNPA as soon as possible, it is important to periodically perform radiological examinations, including chest CT, as well as to perform serological fungal examinations including anti-*Aspergillus* antibody (IgG) testing, several times during the follow-up period for the initial pulmonary disease.

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