Chronic Necrotizing Pulmonary Aspergillosis Complicated by a Cavitory Lesion Caused by *Pulmonary Mycobacterium-avium* Complex Disease

Yoshihiro KOBASHI, Kouichiro YOSHIDA, Naoyuki MIYASHITA,
Yoshihito NIKI and Toshiharu MATSUSHIMA

Abstract

A 66-year-old woman who had undergone one year's treatment for pulmonary nontuberculous mycobacterial disease due to *Mycobacterium avium* (rifampicin, ethambutol, clarithromycin, streptomycin, levofloxacin) five years earlier was admitted to our hospital because of continuous fever and a newly detected abnormal chest shadow, which was like a fungus ball in the right upper lobe on chest computed tomography in the giant cavitory lesion caused by pulmonary *Mycobacterium-avium* complex (MAC) disease. A diagnosis of chronic necrotizing pulmonary aspergillosis (CNPA) complicated by pulmonary MAC disease was made because *Aspergillus niger* was isolated from several sputum specimens, anti-aspergillus antibody was positive, and clinical symptoms such as fever, were disclosed with the radiological finding of a fungus ball-like shadow and an infiltration shadow around the cavity. The patient had received various forms of antifungal chemotherapy, but the clinical effect had been poor. Since then, she had been slowly worsening. Although mycetomas, with the typical appearance of a fungus ball on a chest radiograph, have been reported to easily form in cavitory lesions caused by previous pulmonary tuberculosis, we believe, as illustrated by the present case, that they could also form in such lesions caused by pulmonary MAC disease, since the frequency of pulmonary nontuberculous mycobacterial disease has recently been increasing in comparison with that of pulmonary tuberculosis.
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Key words: pulmonary nontuberculous mycobacterial disease, chronic necrotizing pulmonary aspergillosis, cavitory lesion

Introduction

In patients with underlying pulmonary diseases, even if their general immunity is within normal limits, pulmonary aspergilloma or chronic necrotizing pulmonary aspergilloma (CNPA) with a fungus ball consisting of fibrin, mucus, clusters of cells, and hypha of *Aspergillus* spp. may occur because the conidium of the inhaled *Aspergillus* spp. could not be excluded. Fungus balls form in preexisting cavities of pulmonary tuberculosis, pulmonary cysts or ectatic bronchi. Pulmonary aspergilloma is an important complication occurring with remaining cavities due to old pulmonary tuberculosis, and it has been reported as a complication in 15% of patients with sequelae of pulmonary tuberculosis (1). In a previous report (2), although it was noted that the most frequent underlying disease of pulmonary aspergillosis was pulmonary tuberculosis, there have been no detailed reports regarding the formation of pulmonary aspergilloma including CNPA with a fungus ball in a cavity formed by pulmonary *Mycobacterium avium-intracellulare* complex (MAC) disease during a follow-up period. Herein, we report a peculiar case of CNPA in which a fungus ball appeared in a growing cavity transitionally formed by pulmonary MAC disease during a follow-up period after treatment for the disease was finished.

Case Report

A 66-year-old woman, who had undergone one year's treatment for pulmonary MAC disease (rifampicin (RFP) 450 mg/day, ethambutol (EB) 750 mg/day, clarithromycin (CAM) 600 mg/day, streptomycin (SM) 0.75 g/3 times/week, levofloxacin (LVFX) 300 mg/day) diagnosed according to the diagnostic criteria for pulmonary MAC disease of the American Thoracic Society (3) five years earlier, was ad-

From the Division of Respiratory Diseases, Department of Medicine, Kawasaki Medical School, Kurashiki
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Reprint requests should be addressed to Dr. Yoshihiro Kobashi, the Division of Respiratory Diseases Department of Medicine, Kawasaki Medical School,
577 Matsushima, Kurashiki 701-0192

Table 1. Laboratory Data on Admission

Peripheral blood		Serology	
RBC	395×10 ⁴ /μl	IgG	1,690 mg/dl
Hb	11.1 g/dl	IgA	618 mg/dl
Ht	34.9%	IgM	303 mg/dl
WBC	5,920/μl	CHA	×64
Band	1%	<i>Candida</i> antigen	×2
Seg	77%	<i>Aspergillus</i> antigen	(-)
Eosino	1%	<i>Aspergillus</i> antibody	(+)
Mono	7%	<i>Cryptococcus</i> antigen	(-)
Lym	14%	β-D-glucan	7.4 pg/ml
Plate	29.9×10 ⁴ /μl	CEA	6.8 ng/ml
ESR	113 mm/h	CA19-9	123.7 U/ml
Chemical screening		SCC	2.0 ng/ml
TP	7.9 g/dl	SLX	40.6 U/ml
Alb	3.8 g/dl	CYFRA	2.0 ng/ml
Glb	4.1 g/dl	Sputum	
BS	110 mg/dl	Bacteria	N.F.
Bil (T)	0.3 mg/dl	Fungus	<i>Aspergillus niger</i> (+)
ALP	284 IU/l	AFB	Smear G8
Cho	165 mg/dl		Culture (+++) (2 week)
γ-GTP	20 IU/l		(DDH: <i>Mycobacterium avium</i>)
LDH	233 IU/l	Cytology	Class II
ChE	187 IU/l	Urine	
GPT	8 IU/l	Blood	(-)
GOT	18 IU/l	Sugar	(-)
Crn	0.42 mg/dl	Protein	(-)
BUN	8 mg/dl	PPD	5×5
UA	3.2 mg/dl		15×10
Amy	43 IU/l	Arterial blood gas analysis (room air)	
CRP	4.69 mg/dl	pH	7.401
Na	139 mEq/l	PaO ₂	85.2 mmHg
K	4.6 mEq/l	PaCO ₂	40.0 mmHg
Cl	100 mEq/l		

mitted to our hospital on October 7, 2003 because of continuous fever and a newly detected abnormal chest shadow. She had no other underlying disease, occupational history or drinking history.

On admission, her height was 156 cm and weight 41 kg. Her pulse rate was 102/min and her blood pressure was 144/70 mmHg. Her body temperature was 37.8°C and her respiratory rate was 20/min. Bronchial breath sounds were heard in the right upper lung field, but there were no abnormal findings on other physical examinations. Laboratory data results on admission are shown in Table 1. They revealed a mild anemia and an inflammatory response without leukocytosis. Although serological examinations showed the level of β-D-glucan to be within normal limits, aspergillus antibody was positive. Tumor markers, such as carcino-embryonic antigen (CEA), carbohydrate antigen 19-9 (CA19-9), squamous cell carcinoma-related antigen (SCC), and sialyl stage specific embryonic antigen-1 (SLX), were also mildly elevated. In addition, *Aspergillus niger* was isolated from the same sputum specimens. Purified protein derivative (PPD) was mildly positive. A chest radiograph in

December 1998 revealed an infiltration shadow with a cavitary lesion in the right upper lung field (Fig. 1). Chest computed tomography (CT) in December 1998 disclosed an infiltration shadow with two cavities (1×1 cm in size) in the right upper lobe and micronodular and patchy shadows mainly in the right middle and left lingular lobes (Fig. 2). A chest radiograph on admission (on October 7, 2003) revealed a growing cavity transitionally formed by pulmonary MAC disease with a thick wall (8 cm in size) in the right upper lung field and worsening of the inhomogeneous infiltration shadow in the right and left middle and lower lung fields (Fig. 3). Chest CT on this admission revealed a growing cavitary lesion with a fungus ball-like shadow (10×8 cm in size), an infiltration shadow around the cavity in the right upper lobe and worsening of micronodular and patchy shadows mainly in the right middle and lower lobes and left lingular lobes (Fig. 4).

We made a diagnosis of CNPA with the fungus ball in the cavitary lesion of the right upper lobe as a complication of pulmonary MAC disease due to *Mycobacterium avium* because *Aspergillus niger* was isolated from several sputum

Figure 1. Chest radiograph in December 1998 showing an infiltration shadow with a cavitary lesion in the right upper lung field (2 cm in size) and inhomogeneous shadows in the right and left middle and lower lung fields.

specimens and anti-aspergillus antibody was positive. She had received Micafungin (MCFG) antifungal agents 150 mg/day for CNPA without treatment for pulmonary MAC disease. Although *A. niger* disappeared from the sputum specimens and both her fever and the inflammatory reaction improved, they worsened again two weeks later. Therefore,

the treatment of amphotericin B (AMPH) inhalation therapy 10 mg/day and oral administration of ITCZ 200 mg/day, but her symptoms, inflammatory reaction and radiological finding have not changed. *A. niger* disappeared from her specimens in June 2004.

Discussion

There are few differences in the clinical features of pulmonary nontuberculous mycobacterial disease (especially, pulmonary MAC disease) and those of pulmonary tuberculosis (4), but a slight difference was recently clarified because of advances made in radiological technology, specifically high resolution computed tomography (HRCT). Pulmonary MAC disease radiological findings were classified into three groups (5): 1) features resembling pulmonary tuberculosis, with the characteristic finding being a micronodular shadow with satellite lesions, and cavity formation in segment 1 or segment 2 of the upper lobe, 2) micronodular and trans-bronchial lesions, with the characteristic finding being aggregation of subpleural micronodules and thickening or dilatation of the bronchus in the middle and lingular lobes in middle-age women, but with few nodules with cavities, and 3) third group with disseminated lesions throughout the whole body, with the characteristic finding being only mediastinal lymphadenopathy and few abnormal findings in the lung. The case reported here corresponded to the group having features resembling pulmonary tuberculosis. The cavity which had formed five years earlier had formed in an enlarged cavity surrounded by an infiltration shadow.

Regarding the underlying diseases of pulmonary aspergillosis including CNPA, it has most frequently been reported as a sequela of pulmonary tuberculosis (25–72%), secondary to a preexisting intrapulmonary cavity such as a pulmonary cyst or an ectatic bronchus (2, 6–8). To the best of our

A

B

Figure 2. Chest Computed tomography in December 1998 showing an infiltration shadow with two cavities (1×1 cm in size) in the right upper lobe (A) and micronodular and patchy shadows mainly in the right middle and left lingular lobes (B).

Figure 3. Chest radiograph on admission showing a growing cavitory lesion with a thick wall (8 cm in size) in the right upper lung field and worsening of an inhomogeneous infiltration shadow in the right and left middle and lower lung fields.

knowledge, there have been no reports precisely describing the appearance 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 *Mycobacterial xenopi* (9, 10). However, the frequency of nontuberculous mycobacterium (MAC, etc.) has been recently

increasing among patients with pulmonary mycobacterial diseases, especially in industrialized nations (3). In addition, there actually may have been many cases in previous reports in which the underlying disease of pulmonary aspergilloma including CNPA was a cavity formed by a pulmonary nontuberculous mycobacterial disease rather than one formed by pulmonary tuberculosis.

The clinical symptoms caused by pulmonary aspergilloma vary with the severity of the underlying preexisting pulmonary disease, but a common characteristic has been hemoptysis. This case presented with the chief complaint of continuous fever suspected to be a general symptom. Because the chief complaint was continuous fever in this case, we think that she might actually have had semi-invasive pulmonary aspergillosis, which comparatively suddenly destroyed the lung, or chronic necrotizing pulmonary aspergillosis (CNPA) rather than pulmonary aspergilloma (11, 12). Denning also reported that pulmonary aspergilloma patients with clinical symptoms such as fever and cachexia were diagnosed with CNPA rather than pulmonary aspergilloma (13). Although her patient had a mixed infection caused by *A. niger* and *M. avium*, we cannot rule out the possibility of invasion by *A. niger*, surrounding the cavity in this case. It has been commonly mentioned that *A. fumigatus* is most frequently isolated from patients with pulmonary aspergilloma or CNPA. Kawamura et al (2) and Perfect et al (14) reported that the isolation rate of *A. fumigatus* was 75% and 80%, respectively, while that of *A. niger* was 9% and 10%.

Regarding the laboratory findings, it has been reported mentioned that tumor markers (CEA, CA19-9, SCC, SLX) are often elevated in several benign diseases containing pulmonary mycobacterial diseases and the percentage of these tumor marker elevation is 15–62% (15, 16). Histologically, because these tumor markers were expressed in mucous cells

A

B

Figure 4. Chest computed tomography on admission showing a growing cavity with a fungus ball-like shadow (arrowhead, 10×8 cm in size), an infiltration shadow around the cavity in the right upper lobe (A), and worsening of micronodular and patchy shadows mainly in the right middle and lower lobes and left lingular lobe (B).

of the bronchial gland and surface of the bronchiolar surface epithelium cells (17), it was suspected that serum tumor markers increases in the cases of hyperplasia of the bronchiolar epithelium cells or the mucous cells of the bronchial gland existed in our case because of chronic respiratory infection with bronchiectasis due to pulmonary MAC disease.

As for the clinical diagnosis, since we carefully watched for any complications of CNPA during our five-year follow-up of the patient, we were able to make a diagnosis of CNPA based on the radiological finding of a small fungus ball-like shadow with an infiltration shadow around the cavity, a positive anti-aspergillus antibody reaction, and frequent isolation of *A. niger* from sputum specimens.

Regarding treatment, because there is no significantly effective therapy for pulmonary MAC disease as an underlying pulmonary disease (18), as in most patients, the disease has been slowly progressive in this patient. Although surgical resection of the cavitary lesion caused by CNPA is the recommended treatment method, most patients with CNPA undergo conservative therapy, such as antifungal chemotherapy, because of adhesion of the pleura or lower respiratory function. In our case, there was no good clinical effect even with intravenous drip infusion or MCFG and inhalation of AMPH. Therefore, this patient was followed up with oral administration of ITCZ. Recently, new antifungal agents have developed including azole and echinocandin antifungal agents (19, 20), which possess high antifungal activity for *Aspergillus* spp. However, the clinical effect on pulmonary aspergilloma including CNPA with a fungus ball-like shadow is not expected to be good because the transitional rate of antifungal agents in the cavity is poor. Although direct local injection of AMPH by a transcutaneous or transbronchial route has been reported to be effective for the treatment of pulmonary aspergilloma including CNPA (21, 22), there have been many problems with regard to complications and usefulness.

We encountered a peculiar case which was diagnosed as CNPA with a fungus ball in a growing cavity and an infiltration shadow around the cavity transitionally formed by pulmonary MAC disease during a five-year follow-up period. The present case serves as a reminder that pulmonary nontuberculous mycobacterial disease has become one of the underlying pulmonary diseases complicated by CNPA. In order to quickly detect CNPA with a fungus ball as a complication, we consider it important to periodically perform radiological examinations; e.g., chest CT, serological examinations such as ones of anti-aspergillus antibody, and sputum culture examinations during the follow-up period of an underlying respiratory disease.

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