

## Original Article

# Pathophysiological Study of Chronic Necrotizing Pulmonary Aspergillosis

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(Received April 1, 2008. Accepted August 15, 2008)

**SUMMARY:** The aim of the present study is to define the characteristics of the clinical and histopathological features of chronic necrotizing pulmonary aspergillosis (CNPA) cases with severe hemoptysis. We conducted a histological study of three patients clinically diagnosed as having CNPA who had hemoptysis for 5 years. A tuberculosis sequelae was found as the underlying disorder in all three cases. All patients had fever, general fatigue, and hemoptysis, and their chest computed tomographic images revealed fungus balls, cavity wall thickening, consolidation surrounding the cavity, and satellite foci. All had been treated with anti-fungal drugs and corticosteroids. However, all patients died from respiratory failure due to massive hemoptysis. Histopathological examination revealed that the cavity wall consisted of three layers comprised of necrotic, granulation, and fibrous tissue layers. *Aspergilli* were found in both the fungus ball and necrotic tissue comprising the inner layer of the cavity. In addition, most of the vessels were incompletely occluded with thrombosis and were necrotic, as well as showing local invasion of *Aspergilli*. Surgical intervention should be considered as a prior procedure for CNPA patients, because vessels at the cavity wall, whether occluded completely or incompletely, are usually necrotic and/or show local invasion of *Aspergilli*.

## INTRODUCTION

Binder et al. (1) defined the term chronic necrotizing pulmonary aspergillosis (CNPA) to describe the state between aspergilloma and invasive pulmonary aspergillus. Although several recent reports have led to a better understanding of the clinical features of CNPA (2), its pathological features and mechanisms of hemoptysis still remain obscure. To obtain a detailed understanding of the pathophysiology of CNPA and hemoptysis as its serious complication, both the clinical courses and histological alterations observed in three autopsies of CNPA were examined. These three cases had been transferred from non-invasive aspergillosis of fungal ball type occurred in sequelae of pulmonary tuberculosis.

## PATIENTS AND LABORATORY INFORMATION

**Case 1:** A 67-year-old man with sequelae of pulmonary tuberculosis and hepatitis C virus (HCV)-related liver cirrhosis was admitted to our hospital in October 2001 with a 4-month history of cough, hemoptysis, wheezing, and dyspnea. Physical examination revealed a body temperature of 37.4°C, blood pressure of 134/86 mmHg, and pulse rate of 68/min with an irregular rhythm. The auscultation indicated wheezing in the bilateral lung fields. The laboratory data revealed a leukocyte count of 3,800/ $\mu$ l with 62.5% neutrophils, a platelet count of  $9.4 \times 10^3$ / $\mu$ l, and PaO<sub>2</sub> of 64 torr and PaCO<sub>2</sub> of 62 torr on room air. Serum precipitation antibody for *Aspergillus* was positive, and  $\beta$ -D-glucan was elevated at 247 pg/ml. *Aspergillus* galactomannan was not examined. The chest X-ray showed pleural thickening in the right upper lung field (Fig. 1a). Chest computed tomography (CT) scan revealed a mycetoma of 20 × 18 mm in size within the thick-walled

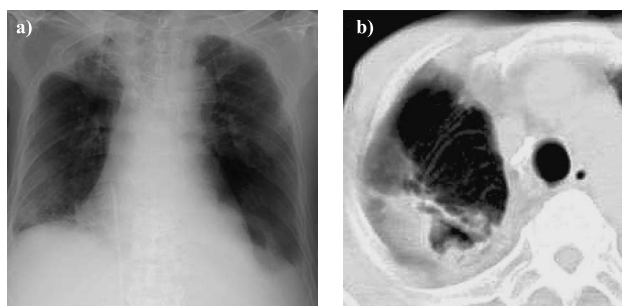


Fig. 1. (a) Chest radiograph on admission showed pleural thickening in the right upper lung field (Case 1). (b) Chest CT showed a mycetoma of 20 × 18 mm in size within the cavity, the wall of which was thickened and had invaded the surrounding parenchyma (Case 1).

cavity which was encompassed with consolidation (Fig. 1b). No mycetomas were isolated from the sputum and no fungal, bacterial, and mycobacterial pathogens were found. He was started with a single 200-mg dose of oral itraconazole (ITCZ) and 40-mg dose of prednisolone for complications of bronchial asthma. On the 20th day after the initiation of the treatment, chest X-ray revealed progressive ground glass opacities in the bilateral lower lung fields. He was administered a high dose of intravenous corticosteroid under the diagnosis of suspected drug-induced ITCZ-induced interstitial pneumonia. After receiving intravenous corticosteroid pulse therapy, the clinical symptoms and chest CT images temporarily improved. However, on the 80th day, the patient died of respiratory failure caused by massive hemoptysis.

**Case 2:** A 77-year-old man with sequelae of pulmonary tuberculosis was admitted to our hospital in March 2000 with a 4-month history of fever, hemoptysis, and dyspnea. He had been treated with oral antibiotics beginning 3 months before admission. The chest X-ray showed a cavity in the left upper lung field. Physical examination revealed a body temperature of 38.2°C, blood pressure of 110/64 mmHg, and pulse rate of 96/min with regular rhythm. The auscultation indi-

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cated coarse crackles in the bilateral lung fields. Laboratory data revealed a leukocyte count of  $7,200/\mu\text{l}$  with 82.5% neutrophils,  $\text{PaO}_2$  of 64 torr and  $\text{PaCO}_2$  of 62 torr on 50% oxygen mask. Sputum culture isolated *Mycobacterium avium* complex. The serum precipitation antibody for *Aspergillus* was positive, and  $\beta$ -D-glucan and galactomannan were elevated at 21.8 pg/ml and 2.5 ng/ml, respectively. Chest X-ray showed a cavity with thickening of the adjacent pleura in the left upper lung field and consolidation in the right upper and middle lung fields (Fig. 2a). Chest CT scan revealed a mycetoma of  $28 \times 18$  mm in size within the cavity, and the consolidation was confirmed with air bronchograms (Figs. 2b, 2c). He was started with a single 10-mg dose of intravenous AMPH-B (amphotericin-B deoxycholate 0.25 mg/kg body weight), 200-mg of oral ITCZ, 200-mg of oral sparfloxacin, and 800-mg of oral erythromycin. After the initiation of these treatments, the clinical symptoms improved and the chest CT showed significant improvement of consolidation and a decrease in the size of the mycetoma. Just before death, no acid-fast bacilli were found in the sputum. However, on the 44th day after treatment, he died of refractory respiratory failure caused by the sudden onset of massive hemoptysis.

**Case 3:** A 77-year-old woman with sequelae of pulmonary tuberculosis and HCV-related liver cirrhosis was admitted to our hospital in March 2004 with a 1-month history of fever,

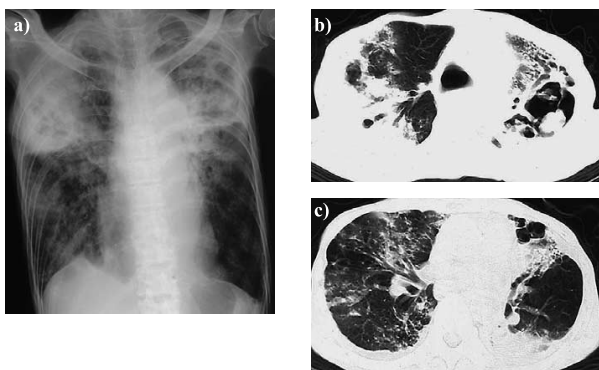


Fig. 2. (a) Chest radiograph revealed a cavitory lesion in the left upper lung field and infiltrative shadow in the right upper and middle lung fields (Case 2). (b), (c) Chest CT showed a fungus ball in the cavity in the left upper lobe and consolidation in the right upper and middle lobes (Case 2).

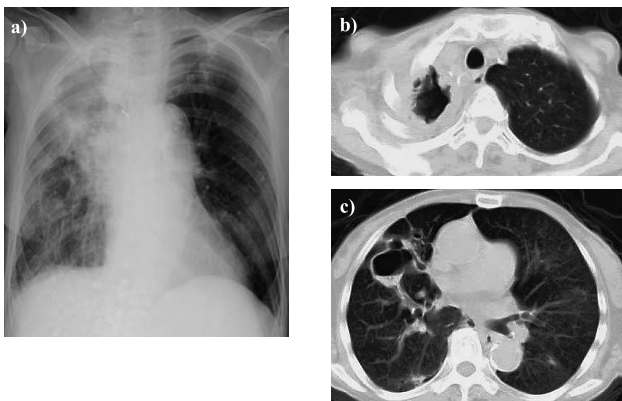


Fig. 3. (a) Chest radiograph showing a cavitory lesion in the right upper lung field and infiltrative shadow surrounding the cavitation (Case 3). (b), (c) Chest CT scan showing a cavity with adjacent pleural thickening in the right upper lobe and cavitory infiltrates with fluid collection in the middle lobe (Case 3).

hemoptysis, and dyspnea. She had a temperature of  $37^\circ\text{C}$ , blood pressure of 134/70 mmHg, and pulse rate of 90/min with a regular rhythm. The chest auscultation revealed coarse crackles in the bilateral lung fields. Laboratory data revealed a leukocyte count of  $11,500/\mu\text{l}$  with 70.5% neutrophils, a platelet count of  $9.4 \times 10^3/\mu\text{l}$ , and  $\text{PaO}_2$  of 54 torr and  $\text{PaCO}_2$  of 42 torr on room air. Culture of sputum was negative for fungal, bacterial, or mycobacterial pathogens. Serum precipitation antibody for *Aspergillus* was positive and  $\beta$ -D-glucan was elevated at 27.4 pg/ml, but galactomannan was not elevated (0.2 ng/ml). Chest X-ray showed a cavity with adjacent pleural thickening in the right upper lung field and consolidation in the right upper and middle lung fields (Fig. 3a). Chest CT scan revealed a cavity of  $70 \times 55$  mm in size and the consolidation was confirmed (Figs. 3b, 3c). She had been treated with a single 150-mg dose of micafungin and 20-mg of prednisolone for the organizing pneumonia. After the initiation of antifungal treatment, the clinical symptoms and chest CT findings were improved. However, on the 37th day the patient died of respiratory failure resulting from massive hemoptysis.

## RESULTS

**Case 1:** Macroscopic examination of the right upper lobe revealed a cavity of 50 mm in diameter, which was filled with a fungus ball and coagulated exudate (Fig. 4a). Histological examination revealed that the cavity wall was composed of three concentric circular layers: necrotic, granulation, and fibrous tissue layers arranged from the luminal position (Fig. 4b). Numerous hyphae were present in the fungus ball and necrotic tissue, and some had invaded into blood vessels (Fig. 4c).

**Case 2:** Macroscopically, a cavity measuring  $50 \times 40$  mm in size was found at the section of the left upper lobe which was filled with coagulated bloody exudate corresponding to a mycetoma (Fig. 5a). Numerous hyphae were confirmed by histological examination in the coagulation of exudate (Fig. 5b). However, a few hyphae were seen as invading organisms into the blood vessels wall (Fig. 5c).

**Case 3:** Macroscopic examination showed a thin-walled

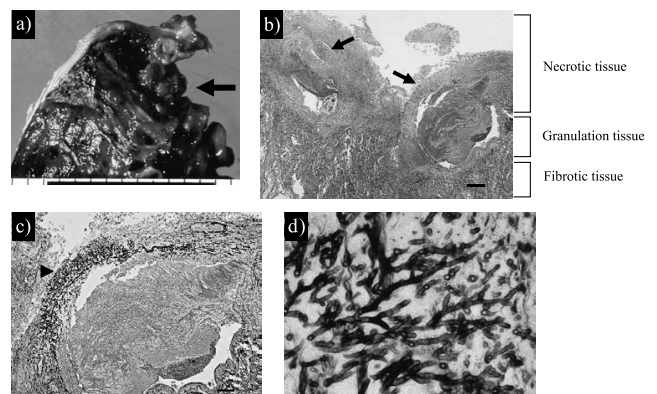


Fig. 4. (a) Macroscopic appearance of the right upper lobe demonstrated a cavity 50 mm in diameter, which was filled with a fungus ball and necrotic materials (arrow) (Case 1). Scale: 1 division = 0.5 cm. (b) Histopathological appearance of the cavity wall revealed three layers, which were of necrotic, granulation and fibrotic tissue (arrows) (Hematoxylin-Eosin stain). Scale bar =  $250 \mu\text{m}$ . (c) Many fungi had invaded the blood vessel (arrow head) (Grocott's stain). Scale bar =  $200 \mu\text{m}$ . (d) There were numerous *Aspergillus* hyphae with Y-shaped branching.

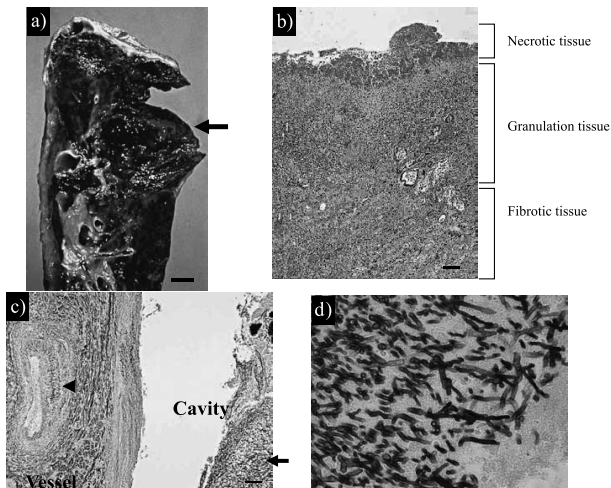


Fig. 5. (a) Macroscopic examination of the left upper lobe revealed a cavity 5 cm in diameter, which was filled with a fungus ball and necrotic materials (arrow) (Case 2). Scale bar = 1 cm. (b) Histopathology of the cavity wall revealed three layers: necrotic, granulation, and fibrotic tissue (Hematoxylin-Eosin stain). Scale bar = 150  $\mu\text{m}$ . (c) Many fungi were evident in the fungus ball and in the cavity (arrow), and had invaded into blood vessel (arrow head) (Grocott's stain). Scale bar = 200  $\mu\text{m}$ . (d) There were densely intertwined separated hyphae consistent with *Aspergillus* spp.

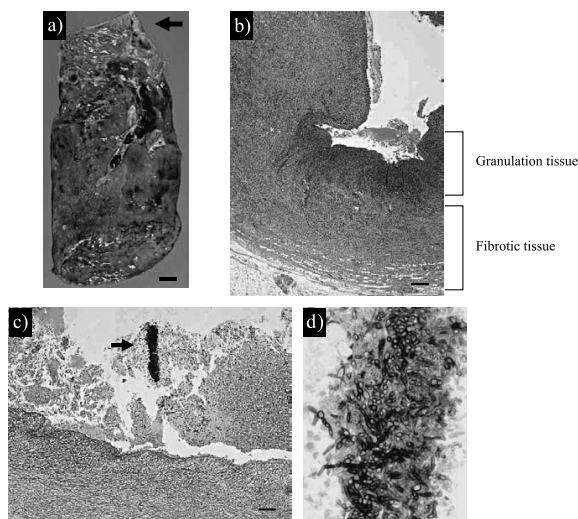


Fig. 6. (a) Macroscopic examination of the right upper lobe revealed a cavity wall 70 mm in diameter (arrow) (Case 3). Scale bar = 1 cm. (b) Microscopic examination of the cavity wall revealed two layers, which were granulation tissue and fibrotic tissue, and the absence of necrotic tissue (Hematoxylin-Eosin stain). Scale bar = 300  $\mu\text{m}$ . (c) Some fungi were noted in the fungus ball (arrow) (Grocott's stain). Scale bar = 170  $\mu\text{m}$ . (d) Fungal elements, showing the branching separated *Aspergillus* hyphae.

cavity of 70 mm in diameter on the section of the right upper lobe (Fig. 6a). Histologically, the cavity wall was comprised of thin and dense fibrous tissue covered with a little necrotic material (Fig. 6b). No hyphae were found as invading organisms in the cavity wall. Hyphae of fungi were limited in the intracavitary mycetoma in the case (Fig. 6c). No fungi were also found in the organizing lesions corresponding to the area of consolidation around the cavity on the chest X-ray.

## DISCUSSION

Binder et al. (1) proposed that CNPA is a disease pattern

that is independent of the pulmonary aspergillosis that characteristically develops in patients with mild immunosuppression, including those with diabetes mellitus, malnutrition, long-term use of low-dose corticosteroids, and collagen vascular diseases such as ankylosing spondylitis and rheumatoid arthritis. Although the clinical course is a chronic process that progresses slowly over several months to years, cavitations occur continuously due to hyphae invading into the tissues, and there is no vascular invasion or dissemination to other organs. This was followed by Geffer et al. (3), who defined semi-invasive aspergillosis as a lesion accompanied by destruction of the lung without fungus invasion of the tissues. As previously mentioned, this form may be accepted as the state during which transformation from the non-invasive form to invasive pulmonary disease occurs.

CNPA usually occurs in middle-aged and elderly patients with underlying lung diseases inducing anatomical remodeling of peripheral airways, such as in chronic obstructive pulmonary disease (COPD), old tuberculosis, pneumoconiosis, cystic fibrosis, and sarcoidosis, and is more likely to develop if the previous anatomical alteration has progressed, such as with inactive tuberculosis with residual cavities (4). The patient usually has fever, cough, sputum, and weight loss of 1 to 6 months duration (4). Radiographic findings show progressive upper lobe cavitory infiltrates associated with pleural thickening. Mycetomas are seen in about half of the patients (5). In the present study, the mean age of the three patients examined was  $73.7 \pm 8.8$  years old. The underlying pulmonary disorders were sequelae of pulmonary tuberculosis in all patients, and two had HCV-related liver cirrhosis as the systemic underlying disease. All presented with chronic cough, hemoptysis, fever, and dyspnea. Chest radiograph revealed a cavity filled with a fungus ball at the upper lobes as a common finding in all patients. Although various histopathological alterations of CNPA have been reported, no histopathological definition has been accepted for diagnosis (2). Therefore, in the present study, the three patients with CNPA were clinically diagnosed in accordance with criteria proposed by Kohno et al. (6). The criteria are: (i) chronic symptoms with fever, cough, hemoptysis, and body weight loss, (ii) chest X-ray and CT scan abnormalities showing infiltrates and cavities in the upper lobes, (iii) positive levels of serum precipitation antibody for *Aspergillus* and  $\beta$ -D-glucan; and/or, (iv) isolation of *Aspergillus* spp. from lung specimens, and (v) failure to detect other bacterial, fungal, or mycobacterial pathogens. According to these criteria, the three patients were diagnosed as having CNPA.

Our pathological examination confirmed fungus balls, including necrotic material within the cavity in which numerous fungi were present. There was, however, an absence of dissemination to other organs observed by autopsy examination. In addition, the lungs in all present cases showed no histopathological findings of bronchopneumonia or nontuberculous mycobacterial pulmonary disease.

Consequently, this suggested that the organization around the cavity may be caused by degenerated exudate disseminated and provided from the mycetoma in the cavity via the airway. The presence of an organizing lesion without fungal components around the cavity is a significantly different characteristic from that of invasive pulmonary aspergillosis (IPA), because the infiltrative shadow in the case of IPA essentially mirrors the filling of acute inflammatory exudates in the alveoli with a fungal proliferation (7,8). Protease and other considerable cytotoxic agents produced by *Aspergilli* (9,10)

may also play a role in producing and increasing the organizing lesion in CNPA. It has been known that long-term corticosteroid administration, diabetes mellitus, and liver cirrhosis impair the function of neutrophils, which play an important role in preventing the invasion of the hyphae of *Aspergilli* from the cavity to the wall covered with epithelium (11).

All of the present patients died of respiratory failure caused by massive hemoptysis. It has been known that massive hemoptysis in the case of IPA is caused by destruction of vessels by direct invasion of *Aspergilli*. However, hemoptysis, understood as bleeding of the peripheral airway, in CNPA may result from invasion of *Aspergilli* in the vessels walls which is limited in necrotic layer of the cavity wall and that lumen is largely occluded by thrombi. Hebisawa et al. (12) reported that hemoptysis occurred in patients with CNPA caused by rupturing of the pulmonary artery, which had been exposed to the luminal surface of the cavity. They assumed that fibrinoid necrosis may weaken the pulmonary arterial wall and that high blood pressure from the bronchial and intercostal arteries may cause the pulmonary artery to rupture. From our observation, an exposure of blood vessels was confirmed, but most of them were occluded incompletely by thrombosis. Therefore, destruction of a plural number of vessels involved by necrosis, local invasion of *Aspergilli*, and the break down of necrotic tissue itself into the cavity may cause bleeding. Moreover, coagulation abnormalities due to liver cirrhosis revealed by the patients of Cases 1 and 3 might be the trigger for hemoptysis.

We surmised that although the clinical signs and data indicate that fungal growth is restrained by antifungal therapy, the patient still is at continuous risk for sudden onset of massive hemoptysis, because the blood vessels, even if they are mostly occluded, may be exposed to the lumen and progressively degenerated by involvement of necrosis at the cavity wall. A coagulation abnormality is commonly associated with such patients. Thus, pulmonary resection is one of the agreeable procedure to improve the outcome for patients with IPA with neutropenia (13,14).

In conclusion, surgical intervention should be considered as a prior procedure for the disease, even though the invasion

of *Aspergilli* is essentially limited to the eroded and necrotic area of the cavity wall in CNPA, because vessels at the cavity wall, whether occluded completely or incompletely, are usually involved by necrosis and/or local invasion of *Aspergilli*, as confirmed by the present study.

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