Superinfection of Chronic Necrotizing Pulmonary Aspergillosis by *Mycobacterium tuberculosis*

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A 63-year-old woman with chronic necrotizing pulmonary aspergillosis complicated by active pulmonary tuberculosis is reported. A small infiltrative shadow appeared, but no definite diagnosis was made. Six years later the shadow was found to have increased in size; chest CT revealed a fungus ball, while a transbronchial lung biopsy revealed aspergillus hyphae. The intrabronchial inoculation of amphotericin B proved ineffective, and a lobectomy was performed. Histopathologic findings showed necrotic granulomas containing aspergillus and some acid-fast bacilli. While the superinfection of healed tuberculous lesions by *Mycobacteria* or *Aspergillus* species is well documented, their coexistence is rare.

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**Introduction**

Chronic necrotizing pulmonary aspergillosis is a discrete clinical entity which is intermediate between aspergilloma and invasive aspergillosis, but is not common in Japan. Only five cases have been reported in Japan as far as we could discover. Although aspergillosis is commonly found in old healed tuberculous cavities, pulmonary aspergillosis is rarely complicated by active pulmonary tuberculosis. The present case was a rare case of superinfection of chronic necrotizing pulmonary aspergillosis complicated by active pulmonary tuberculosis.

**Case Report**

A 63-year-old woman was admitted to Nagasaki University Hospital for examination and treatment. In July 1981 (57 years old), during the course of mass screening for lung cancer, she was found to have a small infiltrative shadow in the right middle lung field (Fig. 1a). Multiple sputum cultures and culture of bronchial aspirates for bacteria, mycobacteria and fungi were negative. Transbronchial lung biopsy showed only nonspecific inflammation. A tuberculin test was positive (9×8/17×14). She was admitted to the hospital for therapeutic diagnosis, and was treated with combination antituberculosis therapy consisting of isoniazide (0.4g/day), rifampicin (0.45g/day), ethambutol (1g/day) and streptomycin (0.75g/day for 4 weeks followed by 1g twice a week for 3 weeks) for 6 months. As a result, the shadow decreased slightly. In October 1987, because of an increased shadow in the chest roentgenogram despite treatment with ofloxacin at a daily dose of 600mg, the patient was readmitted to Nagasaki University Hospital for further evaluation and treatment.

On the second admission her temperature was 36.6°C. Physical examination findings were not remarkable. Laboratory findings, such as peripheral blood count, chemistry, serology and immunological tests, were normal; the white blood cell count was 3,900/mm³. The erythrocyte sedimentation rate at 1 hour was 12mm. CRP was negative. IgG was 1,316mg/dl; IgA 123mg/dl; and IgM 275mg/dl. The OKT4/8 ratio was 1.83. The stimulation index of lymphocyte stimulation tests by phytohemagglutinin and concanavalin A were 2.03 and 1.71, respectively. The sputum smears and cultures were negative for *Mycobacterium* spp. and fungi. Tests for anti-aspergillus antibody were negative by immunodiffusion at 2 different days of admission.

A chest roentgenogram showed an infiltrative shadow in the right S3a, and chest CT revealed a fungus ball in the cavity (Fig. 2a). Sputum specimens and bronchial
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Fig. 1. a) Chest roentgenogram in November 1981 showing a small infiltrative shadow in the right upper lobe. b) A wedge-shaped shadow and a cavity were revealed in February 1988.

Fig. 2. a) Chest CT scan in December 1987 showing a fungus ball in the cavity. b) The wedge-shaped infiltrate was increased by March 1988.

Aspirates were noninformative but a transbronchial lung biopsy (performed in November 1987) revealed aspergillus hyphae suggesting an aspergilloma. Intrapulmonary inoculation of amphotericin B was started at a dose of 0.1 mg/wk, and then increased up to 5 mg/wk for a total dose of 26.1 mg, given over 9 weeks, but was ineffective. The patient developed a low grade fever and cough in February 1988. Chest roentgenogram and CT at that time showed an increased infiltrative shadow in the right S3a (Figs. 1b and 2b). A right upper and middle lobectomy was performed in March 1988 for further examination and treatment.

Lobectomised lung showed a granulomatous lesion (5 cm × 3 cm) with a cavity (1 cm diameter) in the right S3. Histopathologic examination revealed many necrotic granulomas containing numerous aspergillus hyphae and a few acid-fast bacilli in the necrosis, surrounded by giant cells, epitheloid cells and lymphocytes (Fig. 3). After staining, the hyphae were found to be positive immunohistochemically by anti-aspergillus antibody, but the fungal culture of the lesion was negative (Fig. 4). Hyphae were filled in the cavity like mycetoma. There was no aspergillus invasion in the blood vessels, nor was there infarction. Mycobacterium tuberculosis, but no fungi, was isolated from the sputum three times during February and March 1988. These findings suggested a diagnosis of chronic necrotizing pulmonary aspergillosis with active pulmonary tuberculosis. Even though the lesion was lobectomised, isoniazide, rifampicin and ethambutol were readministered for 6 months after
Pulmonary aspergillosis is classified into three distinct entities: the allergic type (such as allergic bronchopulmonary aspergillosis), the saprophitic type (such as aspergilloma), and the invasive type (such as aspergillus pneumonia). It is possible, however, that an overlapping of these entities occasionally occurs, influenced by such factors as the patient’s immune status and lung architecture (1). Limited tissue invasion by aspergillus has been reported in a mildly immunosuppressed patient with allergic bronchopulmonary aspergillosis (2). A fungus ball was observed in the lung cavity of a patient with allergic bronchopulmonary aspergillosis (3). Although invasive aspergillosis would be more likely in an immunocompromised patient, there have been several reports of invasive aspergillosis in apparently immunocompetent hosts (4).

Binder et al suggested that it is a discrete clinical entity, and proposed the designation “chronic necrotizing pulmonary aspergillosis” (5), while Gefter et al proposed it as “semi-invasive pulmonary aspergillosis” (6). It usually occurs in patients with mild immunosuppression or underlying lung disease, and progresses slowly. However, conventional immunological examination of the present patient showed no abnormalities. In such aspergillosis, the fungus is intermediate between a simple saprophyte and an invasive pathogen; its radiographic features include a chronic infiltrate, progressive cavitation, and the subsequent formation of mycetoma.

The major pathologic findings reported in a patient with chronic necrotizing aspergillosis included cavities containing amorphous hyphal aggregates, and some degree of invasion and destruction of the surrounding lung tissue (7). The disease can be distinguished from invasive aspergillosis by the limited parenchymal invasion and the absence of vascular invasion and infarction. The histopathology of the present patient showed that the necrotic tissue in the granuloma was invaded by aspergillus, but there was neither infarction nor invasion of the blood vessel, as is typical of chronic necrotizing aspergillosis.

In Japan, only 5 cases of chronic necrotizing pulmonary aspergillosis have been reported (8–12). The present case is also unusual in that the necrotic granuloma of aspergillosis contained a few acid-fast bacilli in the necrotic foci (ZN, ×600). GMS reveals aspergillus hyphae in the same foci (GMS, ×400).

Since the necrotic granuloma consisted of mainly aspergillus hyphae, it is more likely that aspergillosis was the main lesion with M. tuberculosis superinfection. It is impossible to rule out completely the possibility that the superinfection by non-tuberculous mycobacteria (5). Active tuberculosis was confirmed in the present patient by culture of sputum.
present case was an instance of aspergillosis invading a healed tuberculous lesion, but the pathological features of chronic necrotizing aspergillosis are quite unique and characteristic. Pulmonary superinfection of this disease with *Xanthomonas maltophilia* was reported, but is rare (5).

The treatment of chronic necrotizing pulmonary aspergillosis with antifungal agents is generally favorable, but the present patient did not respond to intrabronchial inoculation of amphotericin B. This could be due to the disconnection of much of the lesion from the bronchus, or possibly due to the infrequency of inoculation. No definite reason was disclosed. Fortunately, surgical resection was effective, and no antifungal chemotherapy was necessary after operation. Even though antituberculous agents were administered, no radiological change was observed.

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**References**