Chronic necrotizing pulmonary aspergillosis following cryptococcal infection of the lung

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Abstract
A 64-y-old male with steroid-induced diabetes mellitus was admitted to our hospital because of a nodular shadow found by chest radiography. Pathological examination revealed pulmonary cryptococcosis, and he was positive for serum Cryptococcus antigen. After oral treatment with fluconazole, he experienced clinical and radiographic improvement, but during ensuing observation without antifungal treatment his respiratory symptoms gradually worsened. Chest radiography showed progressive infiltration around the cavity, and Aspergillus mold was isolated by transbronchial lung biopsy from the lesion where previous cryptococcal infection was present. In addition, serum antibodies to Aspergillus antigens were demonstrated by immunodiffusion. Thus, pulmonary aspergillosis was found to complicate a case of pulmonary cryptococcal infection.

Introduction
Aspergillosis is caused by the mold Aspergillus, and aspergilloma usually occurs in a pulmonary cavity or ectatic bronchus that develops after the occurrence of a previous pulmonary disease such as tuberculosis, sarcoidosis or cystic fibrosis.

Chronic necrotizing pulmonary aspergillosis (CNPA) was originally described as a semi-invasive type of infection [1,2], involving indolent but progressive infection of the lung and resulting in local invasion by Aspergillus mold. Denning et al. proposed a classification of chronic forms of aspergillosis, which involves 3 categories: CNPA, chronic cavity pulmonary aspergillosis (CCPA), and chronic fibrosing pulmonary aspergillosis (CFPA) [3]. We here report on a case of CNPA that occurred in a cured cryptococcal lesion.

Case report
A 64-y-old male was admitted to our hospital because of a nodular shadow found on a routine chest radiograph. He had a history of rheumatoid arthritis treated with corticosteroids for 2 y, and had steroid-induced diabetes mellitus. He had never smoked, never fed animals, and he did not have any respiratory infectious symptoms. The results of a blood analysis were normal, showing a white blood cell (WBC) count of 7400/μl with 65.8% neutrophils. However, his C-reactive protein (CRP) value was elevated to 141.5 mg/l. In addition, his Human T-cell lymphotropic virus (HTLV)-I antibody was negative, and human immunodeficiency virus (HIV) antibody was not tested. A chest radiograph showed a solitary nodular shadow with cavity in the left upper lung field. A chest computed tomography showed a cavity with a thin wall of 2 cm in diameter in S1+2, but no pleural effusion or lymphadenopathy (Figure 1A). Serum glucuronoxylomannan, a cryptococcal antigen (Serdirect® ‘Eiken’ Cryptococcus, Eiken Chemical Co., Ltd, Tokyo, Japan), was positive and pathologically proved as cryptococcosis from a specimen taken by transbronchial lung biopsy (TBLB) (Figure 1A). A cerebrospinal fluid sample showed no abnormal findings.

The patient was diagnosed with pulmonary cryptococcosis and treated with oral itraconazole (ITCZ) 200 mg daily for a month, but a chest radiograph showed no improvement, and the ITCZ treatment was switched to oral fluconazole (FLCZ) 400 mg daily. Over the 6-months FLCZ treatment, the nodular shadow was improved to just a scarred...
lesion, and his serum Cryptococcus antigen level became negative.

However, 2 months after the completion of FLCZ, headache, coughing, yellowish sputum and fever gradually returned. Blood analysis revealed a WBC count of 10,700/μl with 78.8% neutrophils and his CRP value was elevated to 111.5 mg/l. A chest radiograph showed the presence of a progressive and infiltrative shadow around the former cryptococcal infection site (Figure 1B). Recurrent exacerbation of pulmonary cryptococcosis was suspected and oral FLCZ was again started. However, his symptoms worsened and the pulmonary lesion progressed, so treatment with intravenous 0.5 mg/kg/d amphotericin B and 120 mg/kg/d oral flucytosine was started to replace FLCZ. Since he was negative for serum cryptococcal antigen, a bronchoscopic examination was performed 7 d after start of the antifungal

Figure 1A. A cavity with a thin wall 2 cm in diameter in S1+2 was seen. 1B. Progressive infiltrative shadow around the cavitary lesion was observed. 1C. Infiltration disappeared and a thin-walled cavitary lesion was left.

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Figure 2A. A globular spore was observed (HE stain). 2B. A fungal body and mycelia were observed (HE stain).
treatment. Mycelial formation was histopathologically observed in the TBLB samples, in which necrotic change, fungal bodies, mycelia and oxalic acid calcium were found, thus suggesting Aspergillus niger infection. Cryptococcus or significant bacteria were not cultured from the samples. Accordingly, the patient was diagnosed with Aspergillus infection. Itchy eczema was seen on his back and lower extremities, and renal dysfunction was noted by an increased creatinine value 10 d after the antifungal treatment was started. Since we suspected anti-fungal related toxicoderma and renal dysfunction, both flucytosine and amphotericin B treatment were discontinued. The patient subsequently received 300 mg/d oral ITCZ, after which both his clinical symptoms and signs almost disappeared. ITCZ treatment was continued for 6 months, and no relapse was seen 1 y after discontinuation of antifungal treatment.

Discussion

CNPA locally invades the lung tissue for a long period of time [5], and the criteria for clinical diagnosis include growth of Aspergillus sp. from a lung biopsy specimen, bronchoscopic washing, percutaneous lung aspirate or sputum. Another essential aspect is its clinical response to antifungal therapy [5]. Our case met these criteria as well as the pathological criteria of local invasion.

CNPA is usually seen in patients with underlying lung disease [6,7]; however, prior cryptococcal infection as an underlying disease has not been described. This patient showed a worsened condition by chest radiography, pathological and mycological proof of Aspergillus sp. infection, had symptoms such as cough and yellowish sputum, and showed increased blood-inflammatory reactivity, symptoms which are consistent with the proposed criteria for CNPA.

As a confirmatory diagnostic test, determination of serum IgG antibody against Aspergillus should be positive for CNPA during and after the course of aspergillosis. Our patient showed antibodies and was negative for cryptococcal antigen when his second exacerbation was highlighted by chest radiography. Aspergillus spp. were found in the specimen obtained by TBLB at the lesion where cryptococcal infection was previously proven, and the pathological observation of crystals of oxalic acid calcium specifically suggested Aspergillus niger infection.

Voriconazole (VRCZ) is considered the first line antifungal in Aspergillus infection [8]; however VRCZ is not available in Japan as of December 2004, so the common treatment for aspergillosis is still systemic amphotericin B. ITCZ is an effective alternative, but surgical resection could be a promising treatment. Surgery was suspended due to poor general status in our case.

The patient was diagnosed with CNPA following cryptococcosis. We assume that Aspergillus spores had colonized a preexistent cavitary lesion caused by cryptococcal infection, and that Aspergillus infection then occurred in the same lesion. Only rarely 2 different fungi, Cryptococcus and Aspergillus species are shown pathologically and mycologically to exist at the same site. In conclusion, it is necessary to take aspergillosis into consideration when therapeutic failure occurs in a case of cavitary pulmonary lesions caused by yeast infection.

References