Case report

Rapidly progressive pneumonia caused by Cryptococcus neoformans in the patient of granulomatosis with polyangiitis

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Introduction

Cryptococcus neoformans (C. neoformans) is an encapsulated fungus found in soil that is associated with bird droppings, especially pigeons [1–3]. Cell-mediated immunity is essential in controlling cryptococcal infections, and it is considered an opportunistic pathogen because infections occur primarily in patients with profoundly impaired cell-mediated immunity although C. neoformans sometimes infects immunocompetent hosts [2]. Here, we describe rapidly progressive and lobar pneumonia caused by C. neoformans that could be followed up as changes in chest X-ray findings.

Case report

A 57-year-old male who had been treated for granulomatosis with polyangiitis (GPA) presented with cough and back pain that had persisted for three days. Mild infiltration shadows and nodules were found on computed tomography images at that time. Increase of GPA lesions and/or bacterial pneumonia was initially suspected. However, serum Cryptococcus neoformans antigen was positive and the chest X-ray findings had worsened by the following day despite of appropriate antibiotic treatment. Thus, pneumonia due to C. neoformans was diagnosed because C. neoformans was also isolated blood and lung tissues, and he was treated with antifungal agents: L-AMB and 5-FC, and followed up by chest radiography on a daily basis.

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Cryptococcus pneumonia and administered fos-fluconazole (fos-FLCZ) 400 mg/day. Two days later, C. neoformans was cultured from both sputum and blood samples (Fig. 3A).

Although increase of GPA lesions, which make similar granuloma with Cryptococcus infection, was also suspected, we detected significant numbers of C. neoformans by transbronchial biopsy (TBB) of the left lower lobe by bronchoscopy examination (Fig. 3B), and finally diagnosed his main pathogenicity as acute lobar pneumonia by C. neoformans.

We did not detect C. neoformans in cerebrospinal fluid (CSF), which appeared essentially normal (pressure, 140 mm H₂O; cells, 2/μL; protein, 19 mg/dL; glucose, 70 mg/dL) and negative for Cryptococcus antigen, but we changed fos-FLCZ to liposomal-amphotericin B (5 mg/kg/day) plus 5-FC (4 × 25 mg/kg/day) at Day 2, and continued for two weeks followed by fluconazole (200 mg/day) according to severe cryptococcal infection cases. The susceptibility of the isolated C. neoformans to antifungal drugs (minimum inhibitory concentration; MIC) was as follows: AMPH-B (0.5 μg/mL), 5-FC (8 μg/mL), FLCZ (2 μg/mL), VRZ (0.03 μg/mL), and MCFG (>16 μg/mL), respectively, and blood cultures became negative on Day 11.

Signs on chest radiograms worsened until Day 4 (Fig. 1C), but improved daily until day 20 (Fig. 1E and F).

**Discussion**

Disease related to C. neoformans or Cryptococcus gattii has become increasingly prevalent in immunocompromised patients, including those with AIDS, although pulmonary cryptococcosis has been isolated sometimes from apparently immunocompetent patients. Infection with C. neoformans first occurs after inhaling fungal basidiospores. A small focal pneumonitis then develops that may or may not be symptomatic [2,4]. The clinical manifestations of pulmonary cryptococcosis include localized nodular lesions with or without cavitations, segmental pneumonic infiltrates, patchy interstitial or alveolar infiltrates, pleural effusions, hilar masses and thoracic lymphadenopathy [1,4].

Our patient had progressive, localized disease with a mild to moderate systemic inflammatory response and an initial indolent presentation. Chest radiography showed mild nodules and infiltrate on Day 1 that rapidly worsened on Days 2 and 4. These findings suggested acute or its on chronic C. neoformans infection in this patient. He was HIV-negative, but was under corticosteroid therapy for GPA, which is pathologically similar to granulomata and appears as radiographic nodules. His CD4 cell counts decreased to 116/μL because methotrexate had been administered to treat worsening GPA. Thus, he might have been immunocompromised, and susceptible to progressive lobar types of pneumonia. Macrophages and lymphocytes might be inactivated, and levels of immunoglobulin G (IgG), IgA, and IgM in the blood have been decreased [5]. Our patient had low IgG levels (585 mg/dL) which required occasional supplementation, and this factor also might accelerate the progress of C. neoformans pneumonia in this patient. In addition, corticosteroid had increased the level of HbA1c, an indicator of diabetes mellitus, to 8.0% (NGSP), which supported the notion that he was in fact immunocompromised. Symptoms and radiographic signs also worsened in our patient within a few days. Such changes might be
the most rapid among all reports of *C. neoformans* pneumonia [3,4,6,7] although it can progress over days instead of weeks in hosts with extreme immunosuppression such as those with AIDS or under medication with high-dose corticosteroid and/or cyclophosphamide [2].

In this case, we detected *C. neoformans* in sputum, blood, and in TBB specimens of infiltrated lesions. These findings together with laboratory data support the notion that the pathogenicity and radiographic changes were mainly due to *C. neoformans* infection rather than GPA exacerbation. In addition, PR3-ANCA did not change, but levels of cryptococcal antigen, which has rather than GPA exacerbation. In addition, PR3-ANCA did not change, but levels of cryptococcal antigen, which has

Patients with symptomatic cryptococcal pneumonia can present with cough, chest pain, increased sputum production, fever, weight loss and hemoptysis. In contrast, the ratio of patients with asymptomatic pulmonary cryptococcosis is about 30% and infection is incidentally discovered in such patients [2,4]. Biopsy specimens from symptomatic patients with chest radiographic findings indicating malignancy occasionally reveal cryptococcosis. Global ecological studies have found *C. neoformans* in soil samples from around the world in areas frequented by birds, especially pigeons and chickens. Our patient lived close to a park that was populated by flocks of pigeons.

Fluconazole is active against *C. neoformans*, easily administered, and has safe profiles. Candidates for treatment are those with persistent and/or disabling symptoms, multiple nodules or extensive infiltrates on chest X-rays, and/or positive serum cryptococcal antigen findings. However, we administered liposomal AMPH-B and 5-FC according to the severe cryptococcal condition cases. Additional studies are needed to more precisely determine the role of AMPH-B and 5-FC followed by fluconazole in treating severe or rapidly progressive pulmonary cryptococcosis in immunocompromised patients as well as the optimal dosage and duration of therapy. The optimal fluconazole dosage has not been defined. A daily dose of 200–400 mg, and induction with 600 mg for four weeks, followed by 200 mg for 10–12 weeks have been administered [8]. Our patient was treated with oral fluconazole 200 mg/day after two weeks AMPH-B and 5-FC. At the four-month follow up, the general condition of our patient was obviously improved and chest X-rays have repeatedly shown that the mass in the lower lobe lung continues to decrease.

In conclusion, we described rapidly progressive cryptococcal pneumonia that was clinically and radiologically improved by treatment with liposomal L-AMPB and 5-FC. The time course was followed up by chest X-rays to detect radiographic changes. Symptoms appeared only three days before admission and chest X-ray findings became abnormal within a few days thereafter. We detected *C. neoformans* from blood and lung samples, which finally distinguished the infection from GPA exacerbation. However, further studies, including accurate diagnosis of *C. neoformans* and the mechanism of rapid progression under various immunological and microbiological backgrounds are required.

**Fig. 3.** Cryptococcus detected in blood and lung tissues. Unstained yeasts are surrounded by empty space (arrows in blood stained with India ink preparation; magnification ×1000 (A). Yeasts are visualized with Grocott stain in lung tissue samples collected by bronchoscopy; magnification ×400 (B).

**References**

[1] Perfect JR, Dismukes WE, Dromer F, Goldman DL, Graybill JR, Hamill RJ, et al. Clinical practice guidelines for the management of cryptococcal disease: 2010 update by the Infectious Diseases Society of America. Clin Infect Dis 2010;50:291–322.

[2] Perfect JR. Cryptococcus neoformans. Principal and practice of infectious diseases, vol. 2; 2010. p. 3267–303.

[3] Wysham NG, Sullivan DR, Allada G. An opportunistic infection associated with ruxolitinib, a novel janus kinase 1,2 inhibitor. Chest 2013;143:1478–89.

[4] Guy JP, Raza S, Bondi E, Rosen Y, Kim DS, Berger BJ. Cryptococcus pneumonia presenting in an immunocompetent host with pulmonary asbestosis: a case report. J Med Case Rep 2012;28:170.

[5] Hillerdal G, Heckscher T. Asbestos exposure and aspergillosis infection. Eur J Resp Dis 1962;63:420–4.

[6] Chen YG, Lin TY, Lin GM, Lin JC. Pulmonary cryptococcosis infection after monotherapy with gemcitabine. Respir Care 2011;56:339–41.

[7] Johannson KA, Huston SM, Mody CH, Davidson W. Cryptococcus gattii pneumonia. CMAJ 2012;184:1367–90.

[8] Yew WW, Wong PC, Wong CF, Lee J, Chau CH. Oral fluconazole in the treatment of pulmonary cryptococcosis in non-AIDS patients. Drugs Exp Clin Res 1996;22:25–8.