Diagnosis of pulmonary mucormycosis aiding the diagnosis of small cell lung cancer

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Mucormycosis is a rare complication in immunocompromised patients. Antemortem diagnosis of mucormycosis is difficult and often incorrect. We report a case of pulmonary mucormycosis caused by Cunninghamella bertholletiae in an elderly man with interstitial pneumonia. The diagnosis of mucormycosis was established by bronchoalveolar lavage. A coexisting immune deficiency condition was considered. Lung cancer was suspected because of an elevated progastrin-releasing peptide level and bilateral hilar and mediastinal lymphadenopathy; it was diagnosed after performing endoscopic ultrasound-guided fine-needle aspiration. Treatment by intravenous liposomal amphotericin B was effective, but relapse occurred because of bone marrow suppression caused by chemotherapy for lung cancer. Treatment for mucormycosis was resumed, but the patient died of carcinomatous lymphangiosis. Autopsy confirmed the diagnosis of pulmonary mucormycosis and revealed refractory anaemia with small cell lung cancer. Mucormycosis often occurs in immunocompromised patients, but this case is rare because the mucormycosis was diagnosed before the diagnosis of malignancy. Because prognosis is often poor, the possibility of coexisting malignancies should always be investigated in patients with mucormycosis infections.

Introduction

Mucormycosis is a rare but opportunistic fungal infection that occurs in immunocompromised patients. Its antemortem diagnosis is especially difficult. Mucormycosis often carries a poor prognosis, which is particularly poor when the disease is caused by Cunninghamella species (Roden et al., 2005). We report a case of pulmonary Cunninghamella infection with lung cancer and refractory anaemia. Lung cancer was diagnosed after the diagnosis of pulmonary mucormycosis, and refractory anaemia was revealed by autopsy. This is a rare case because mucormycosis was diagnosed before diagnosing the malignancy. The possibility of coexisting malignancies should be investigated without fail in patients with mucormycosis infections.

Case report

A 74-year-old Japanese man with interstitial pneumonia (IP) and pulmonary emphysema, for which no medication had been administered, was admitted with fever, cough and exertional dyspnoea. His haemoglobin A1c levels had recently increased to 6.5 % National Glycohemoglobin Standardization Program (NGSP) derived units [47.2 mmol mol⁻¹, International Federation of Clinical Chemists’ (IFCC) units], but he was not treated for diabetes mellitus. His medical history was significant for previous myocardial infarction, angina pectoris and chronic heart failure. He was a 60-pack-year ex-smoker living in a 70-year-old wooden house and managed a metal-recycling company; thus, he was exposed to fine metal particles. On admission, his vital signs were stable, with ambient oxygen saturation of 94 %. Auscultation revealed a few fine crackles bilaterally in the lower lung fields and coarse crackles in the right upper lung field. The complete blood count was normal. His C-reactive protein level was 3.4 mg dl⁻¹ and his KL-6 was 869 U ml⁻¹. KL-6, a useful serum marker to assess the activity of IP, was determined by electrochemiluminescence immunoassay using a Picolumi 8220 analyser (EIDIA).

Beta-D-glucan, Aspergillus antigen and antibody, and Cryptococcus antigen tests in serum were all negative.

Abbreviations: BAL, bronchoalveolar lavage; IP, interstitial pneumonia; L-AMB, liposomal amphotericin B.
Fever improved following antibacterial treatment, but cough, exertional dyspnoea and the right upper field shadow persisted. Chest radiography (Fig. 1) revealed right upper field infiltration and bilateral interstitial infiltrates of the lower lung fields. Computed tomographic scanning revealed abnormal infiltration around the emphysematous area in the right upper lobe and bilateral interstitial infiltrates in the lower lobes, with bilateral hilar and mediastinal lymphadenopathy. Nodules and pleural effusion were not observed. Cunninghamella species grew on a potato dextrose agar medium plate inoculated with a culture of bronchoalveolar lavage fluid (BALF) from the right upper lobe, and were characterized by broad, irregular, sparsely septate and irregular wide-angle branching hyphae stained with lactophenol cotton blue. In addition, Papanicolaou staining of alveolar lavage fluid (BALF) revealed necrotic tissue with multinuclear giant cells. An immune deficiency condition was suspected with Cunninghamella infection. Lung cancer was suspected because of bilateral hilar and mediastinal lymphadenopathy and an elevated progastrin-releasing peptide level of 1030.0 pg ml$^{-1}$, but bronchoalveolar lavage (BAL) specimens yielded negative results for malignant cells. Therefore, a second bronchoscopy was performed 2 weeks after the first, but the results were the same. The second bronchoscopy induced acute exacerbation of the IP. Methylprednisolone pulse therapy (1 g day$^{-1}$ for 3 consecutive days) was administered, followed by oral prednisolone and intravenous liposomal amphotericin B (L-AMB) [2.5 mg (kg body weight)$^{-1}$ for 1 month], to which the patient responded as evidenced by improvement in the right upper lobe shadow on chest radiography. Seven weeks after the first bronchoscopy, endoscopic ultrasound-guided fine-needle aspiration of the mediastinal lymphadenopathy confirmed small cell lung cancer (stage 3B). Chemotherapy (carboplatin + etoposide) reduced the lymphadenopathy bulk. Chemotherapy induced febrile neutropenia, and the right upper lobe shadow worsened 12 days after chemotherapy. Intravenous cefepime treatment was ineffective; therefore, intravenous L-AMB [2.5 mg (kg body weight)$^{-1}$] was readministered. The patient responded, and the right upper lobe shadow decreased. Intravenous L-AMB was continued until his death. Unfortunately, before initiating a second round of chemotherapy, the patient went into acute respiratory failure. He died 6 months after symptom onset.

Autopsy revealed carcinomatous lymphangiosis in the entire left lung. In the right upper lobe, mucormycosis around the emphysematous area was observed, but malignant cells were undetectable. Mucomycosis was localized only in the right upper lobe. Usual IP was observed in both lungs, and honeycomb changes were particularly noted in the lowerlobes. Bone marrow examination showed refractory anaemia.

The original isolate was sent to the Medical Mycology Research Center, Chiba University, where it was analysed by culture and real-time PCR. We used rDNA genes (internal transcribed spacer region), and Cunninghamella bertholletiae infection was confirmed.

**Discussion**

Mucomycosis is a rare infection caused by fungi of the order Mucorales, with the most common causative organisms being Mucor, Rhizopus, Cunninghamella, Lichtheimia and Apophysomyces species (Roden et al., 2005; Gomes et al., 2011). Cunninghamella species are soil saprobes found mainly in the Mediterranean or subtropical climatic zones. Pulmonary mucomycosis is a rapidly progressive infection that occurs after inhalation of spores into the bronchioles and alveoli. Several studies have shown that the mortality due to mucomycosis in cancer patients is declining with the use of lipid formulations of amphotericin for treatment (Pagano et al., 2009; Hammond et al., 2011). However, among mucormycosis-causing species, Cunninghamella species have the worst prognosis (Roden et al., 2005). The mortality rate of mucomycosis associated with Cunninghamella is 81% (Gomes et al., 2011). Mucomycosis in an immunocompetent patient has good prognosis (Sridhara et al., 2005; Zhao et al., 2009; Lechevalier et al., 2008; Tehmeena et al., 2007; Jayasuriya et al., 2006; Radner et al., 1995). Therefore, a case of mucomycosis in an immunocompetent patient who died, without autopsy, was suspected to have involved a coexisting malignancy or other disease that immunocompromised the patient (Baradkar et al., 2008; Shiva Prasad et al., 2008). A literature review revealed only seven reported cases of mucomycosis in patients with nonhaematological malignancies (Roden et al., 2005). There is a report about a Cunninghamella infection in a patient without underlying disease (Zeilender et al., 1990). There is one report of lung cancer, but this involved rhinocerebral mucomycosis (Schuster & Stern, 1995). A search of the relevant literature in English revealed no cases of pulmonary mucomycosis caused by Cunninghamella species associated with lung cancer.

**Fig. 1.** Chest radiograph taken on admission, showing infiltration of the right upper lung field and bilateral interstitial infiltration of the lower lung fields.
Mucormycosis typically occurs in immunosuppressed hosts, such as those with diabetes mellitus, organ or haematopoietic stem cell transplants, neutropenia and malignancy (Roden et al., 2005; Spellberg et al., 2005). The most common underlying conditions for patients with C. bertholletiae infections are leukaemia (51 %), diabetes mellitus (19 %), non-malignant haematological diseases (16 %), deferoxamine-based therapy (12 %), organ transplantation (9 %), asplenia (7 %), hepatic cirrhosis (2 %), AIDS and intravenous drug abuse (2 %), and chronic pharmacological immunosuppression for treatment of autoimmune disease (2 %) (Gomes et al., 2011). In our case, the patient had small cell lung cancer, diabetes mellitus and refractory anaemia. On admission, the blood cell count was normal, and we do not know when the refractory anaemia occurred.

Diagnosis of mucormycosis is based on the identification of organisms in tissue by histopathology and culture confirmation, but biopsy is difficult because the underlying condition is frequently severe. Although contamination of clinical specimens by ubiquitous environmental Mucorales spores is always a possibility, the value of Mucorales-positive cultures (especially repetitive cultures) remains a critical indication of infection in immunocompromised patients. In one case series, only 25 % of sputum or BAL specimens allowed positive antemortem identification (Kontoyiannis et al., 2000), but our BAL specimens showed twice that level of positive results. Non-BAL specimens were negative for Cunninghamella species.

Successful treatment of mucormycosis requires early diagnosis, reversal of the underlying risk factors, reduction, if possible, of immunosuppression, prompt administration of antifungal therapy, and surgical debridement where applicable. Intravenous amphotericin B is the drug of choice. Several studies have suggested that lipid formulations of amphotericin B, particularly L-AMB, are associated with improved rates of response/survival (Sun & Singh, 2011). After parenteral lipid amphotericin B-based treatment, oral posaconazole as maintenance/secondary prophylaxis is recommended (Kontoyiannis & Lewis, 2011), but this drug is not available in Japan. In this case, we used a low dose of L-AMB. There are similar cases of successful use of low-dose L-AMB in Japan (Tominaga et al., 2010; Mori et al., 2003). The optimal dose of L-AMB varies with patients. Therefore, if a patient does not respond, the dose is increased. In general, antifungal therapy for mucormycosis should be continued until all of the following objectives are attained: (1) resolution of clinical signs and symptoms of infection, (2) resolution or stabilization of residual radiographic signs of disease on serial imaging and (3) resolution of underlying immunosuppression (Spellberg et al., 2009).

We treated lung cancer and mucormycosis simultaneously. If our patient’s respiratory function had remained normal, we might have been able to remove the pulmonary mucormycosis surgically and prolong his life. It may be possible to treat mucormycosis and malignancy together, but successful treatment depends on immune status and renal function as well as the extent of infection.

Acknowledgements

We are grateful to Takashi Yaguchi, Medical Mycology Research Center, Chiba University, for the identification of C. bertholletiae, and Manabu Muto, Department of Gastroenterology and Hepatology Medicine, Kyoto University, for the diagnosis of small cell lung cancer.

References


