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Successfully treated invasive pulmonary aspergillosis in a patient with diabetic ketoacidosis

Case Report

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Abstract: We report herein a case of diabetic ketoacidosis associated with invasive aspergillosis that was successfully treated with liposomal amphotericin-B (L-AMB). Early intervention after confirming the diagnosis of invasive pulmonary aspergillosis is very important, and initiating early treatment with L-AMB can lead to a full recovery.

Keywords: *Invasive pulmonary aspergillosis • Diabetic ketoacidosis • Liposomal amphotericin-B*

1. Introduction

The chances of survival for critically ill patients with fungal infection rely on a timely and appropriate antifungal therapy; therefore, early diagnosis is of critical importance. Among fungal infections, invasive pulmonary aspergillosis is associated with high rates of morbidity and mortality despite antifungal therapy [1-5]. The majority of cases of invasive pulmonary aspergillosis are seen in patients with severe immunocompromised conditions. However, cases have been reported in non-immunocompromised individuals, in whom the infection was associated with alcoholism, diabetes mellitus, steroid therapy, or influenza virus infection [6-9]. Diabetic ketoacidosis is an emergent condition, in which invasive pulmonary aspergillosis has rarely been reported [10-13]. We report herein invasive pulmonary aspergillosis successfully treated with liposomal amphotericin-B (L-AMB) in a patient with diabetic ketoacidosis.

2. Case report

A 53-year-old insulin-dependent diabetic patient was admitted to the hospital with a 1 week history of flu-like symptoms. At the age of 49, she was diagnosed as having type II diabetes mellitus, but the control was poor due to lack of insight about the disease. As the patient had no infectious complications, she had not undergone long-term antibiotic treatment. In the 24 hours before hospital admission, she had developed pyrexia accompanied by vomiting and confusion and consequently omitted her insulin. Her husband and daughter had been diagnosed as having influenza-A a few days prior to her admission. On admission she had a temperature was 38°C, a pulse of 126/min, blood pressure of 114/70, and a respiratory rate of 28/min, and she was ketotic. Swab tests for influenza A and B were negative. Her chest was clear and she had no focal neurological signs. Initial blood electrolytes were as follows: sodium 140 mEq/L, potassium 5.4 mEq/L, blood urea nitrogen 95 mg/dL, creatinine 1.66 mg/dL, glucose 716 mg/dL, and Hba1c 10.1%. Arterial blood gas (room air) was as follows: pH 7.229 $PaCO_2$, 18.1 Torr, PaO_2, 85.2 Torr, and HCO_3^- 7.4 mEq/L. The chest radiograph at admission demonstrated infiltrates in the middle and lower zones of both lungs (Figure 1). A chest CT scan showed nodules with the halo sign and focal ground-glass opacity. Some nodules had cavitation (Figure 2). Diabetic ketoacidosis was diagnosed, and she was treated with intravenous fluid and insulin. Intravenous ampicillin sodium/sulbactam and peramivir were commenced because of her pneumonia and possible influenza. Her blood sugar, urea, and acidosis all gradually

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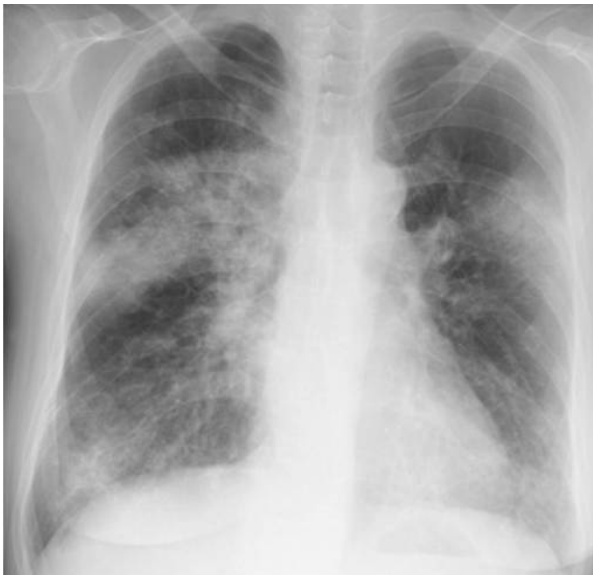

Figure 1. The initial chest radiograph revealed multiple infiltrates in both lungs.

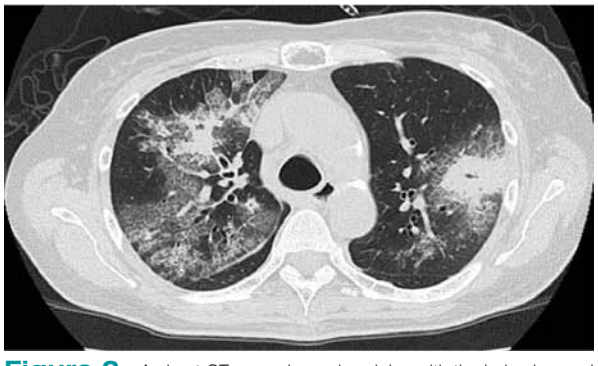

Figure 2. A chest CT scan showed nodules with the halo sign and focal ground glass opacity. Some nodules had cavitation.

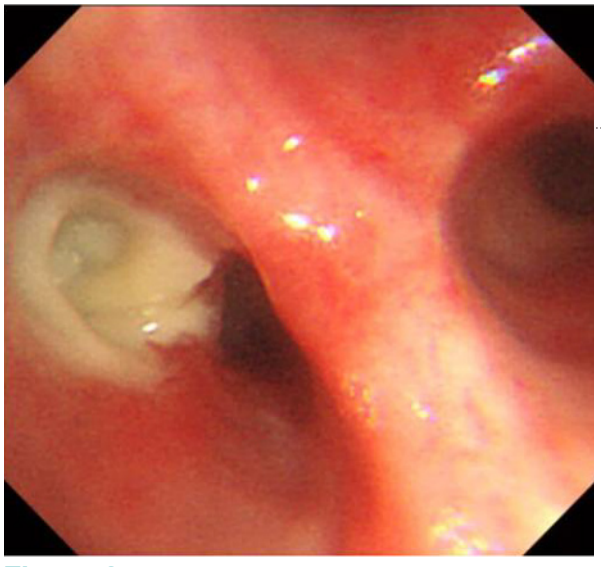

Figure 3. Bronchoscopy showed thick white plaques over the right B3 bronchus, thought to be consistent with aspergillosis.

improved, and neurological recovery was achieved over the next 24 hours. The repeat chest radiograph showed deterioration of consolidation in both lungs. Bronchoscopy showed thick white plaques over the right B3 bronchus, which was thought to be consistent with aspergillosis (Figure 3). Bronchoalveolar lavage and a bronchial biopsy specimen revealed a mass of fungal hyphae, which were both branching and septate and consistent with aspergillosis (Figure 4). Serum antibody to *Aspergillus* (Ouchterlony test) was negative, but serum beta-D-glucan was elevated, at 41.6 pg/mL (upper limit: 20.0 pg/mL). Therefore, the antibacterial agent was changed to L-AMB (100 mg/body per day) and continued for 1 month. She made a good clinical recovery and the serum beta-D-glucan returned to the normal range (10.4 pg/mL). A follow up chest radiograph at the time of discharge showed disappearance of the infiltrates in both lungs (Figure 5).

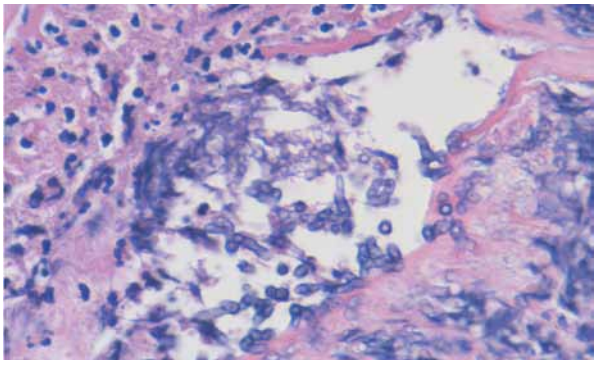

Figure 4. A bronchial biopsy specimen revealed a mass of hyphae, which were both branching and septate and consistent with aspergillosis.

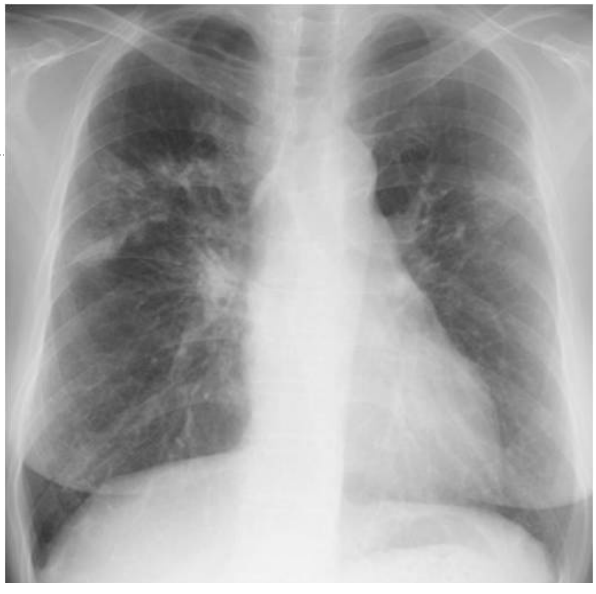

Figure 5. A follow up chest radiograph at the time of discharge showed disappearance of the infiltrates in both lungs.

3. Discussion

Opportunistic infections are common in patients with diabetes mellitus, particularly in those with insulin-dependent diabetes. *In vitro* studies have shown decreased leukocyte bactericidal activity and impaired macrophage mobility and phagocytic capacity [14]. These factors, which are all involved in immune defenses against fungal invasion [15], may predispose diabetic patients to infection. Among opportunistic infections, however, invasive pulmonary aspergillosis is rare in patients with diabetic ketoacidosis [10-13]. We showed herein such a patient, who was successfully treated with L-AMB. To the best of our knowledge, only 4 cases of invasive pulmonary aspergillosis with diabetic ketoacidosis have been reported [10-13]. In 1981, Grizzanti et al reported a 57-year-old female patient with diabetic ketoacidosis and invasive aspergillosis [10]. They treated her with amphotericin-B, and at discharge from the hospital, she was asymptomatic and her chest radiograph was normal [10]. Subsequently, Janes et al presented a 45-year-old male patient, who was successfully treated with amphotericin-B colloidal dispersion, L-AMB [11]. In a case reported by De Rosa et al, a 57-year-old patient was successfully treated with amphotericin B and caspofungin [12]. Very recently, Vaschetto et al reported a 22-year-old male patient who was treated with voriconazole, but the patient died despite intensive therapy [13]. In our patient, we found no other risk factors such as immunosuppressive conditions or hematological malignancies, besides diabetes mellitus.

The radiological appearance of invasive pulmonary aspergillosis includes rounded densities, and pleural-based infiltrates [16,17]. In these patients, multiple nodules with or without the halo sign [16] and cavitating nodules [17] were found in the chest CT scan. In our patient, the initial chest radiograph revealed bilateral multiple infiltrates, and a chest CT scan showed pleural-based infiltrates with or without the halo sign as well as cavitation in some nodules.

The diagnostic approach for invasive pulmonary aspergillosis is not easy. Sputum cultures may be negative. If possible, the presence of *Aspergillus* in a smear or culture of the sputum or respiratory secretions is not necessarily indicative of invasive infection since these organisms are ubiquitous in the environment and can colonize the respiratory tree. The diagnosis of invasive pulmonary aspergillosis is definite when the histopathology shows hyphae, with or without a positive culture for *Aspergillus* from the same site, or a positive culture following percutaneous needle aspiration or open lung biopsy [3]. Bronchoalveolar lavage and transbronchial biopsy are indicated and useful in high risk patients when the organism has to be identified quickly by smear. However, aggressive approaches to lung biopsy in immunocompromised hosts with 'fever and pulmonary infiltrate' syndromes, expedite diagnosis of fungal pneumonias and may improve the high morbidity and mortality [18-20]. In our patient, bronchoscopy could be performed. Diagnosis was achieved by positive Gram staining of the septate, hyaline, branching hyphae in specimens from the bronchoalveolar lavage and transbronchial lung biopsy.

The treatment of choice for invasive aspergillus infection is amphotericin B [21]. Itraconazole may be active against *Aspergillus* species; however, its oral usage achieved poor absorption and, hence, suboptimal serum and tissue levels [22]. In the study by Denning et al [23], only 11% of 51 patients with invasive aspergillosis achieved clinical, radiographical, and mycological cure by oral itoraconazole therapy. Fluconazole has negligible activity in these infections. Three of the 4 patients with invasive pulmonary aspergillosis and diabetic ketoacidosis described above were successfully treated with amphotericin-B [10-12].

This case illustrates an unusual complication of diabetic ketoacidosis. The combination of a recent influenza infection combined with diabetic ketoacidosis likely provided the setting for colonization [24,25] and subsequent invasion of the lung parenchyma by *Aspergillus*. Our patient was negative for *Aspergillus* antibody, implying that the patient was in an immunosuppressive state and the fungal infection was neither subacute nor chronic one. We determined that the normalization beta-D-glucan serum levels indicated the recovery from aspergillosis.

Early intervention after confirming the diagnosis of invasive pulmonary aspergillosis is very important, and initiation early treatment with L-AMB can lead to full recovery from the disease.

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