Surgical Resection and Liposomal Amphotericin B to Treat Cavitary Pulmonary Zygomycosis in a Patient With Diabetes

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We describe a 24-year-old man with type 1 diabetes mellitus and a cavitary lesion in the right upper lobe, caused by a zygomycete. Surgical resection plus liposomal amphotericin B therapy was successful. We discuss predisposing condition, clinical findings, diagnosis, and treatment of pulmonary zygomycosis. *Key words: zygomycete; pulmonary zygomycosis; diabetes; cavitary pulmonary lesion.*
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Introduction

Zygomycosis is a group of mycoses caused by filamentous fungi in the class zygomycetes. Zygomycoses are severe angio-invasive fungal infections that develop in immunocompromised and diabetic patients. Pulmonary zygomycosis results from inhalation of sporangiospores into the bronchioles and alveoli, leading to pulmonary infarction and necrosis with cavitation.[1]

Case Report

We saw a 24-year-old man who was a known diabetic for 4 years and was on oral hypoglycemics. He was a farmer by profession, and presented with dyspnea, cough, and low-grade fever of 4 months duration. Prior to admission he was treated for pneumonia in another hospital, but his symptoms did not improve so he was referred to our tertiary-care hospital.

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On admission, his temperature was 36.9° C, blood pressure 103/69 mm Hg, heart rate 82 beats/min, respiratory rate 21 breaths/min, and S_{pO_2} 100% on room air. Breath sounds were decreased over the right upper lobe.

Laboratory tests revealed a serum glucose range of 11–22 mmol/L, white-blood-cell count of 23×10^9 cells/L, erythrocyte sedimentation rate of 34 mm/h, and creatinine of 45 μmol/L. Other test results were in the normal range. We suspected pulmonary tuberculosis and began anti-tuberculosis medications, including isoniazid, rifampicin, pyrazinamide, and levofloxacin. But his sputum and bronchoalveolar lavage specimens were negative for acid-fast bacilli on smear and after prolonged culture.

Radiograph showed a large shadow of consolidation in the right upper lobe, and computed tomogram showed cavitary consolidation in the right upper lobe (Fig. 1). Bronchoscopy revealed a nodular growth completely obstructing a right-upper-lobe bronchi (Fig. 2), and biopsy revealed an inflammatory cell infiltrate and organisms that appeared as broad, nonseptate hyphae (Fig. 3). The diagnosis was pulmonary zygomycosis, and we initiated intravenous liposomal amphotericin B, and discontinued the anti-tuberculosis agents. No other localizations of zygomycosis were found.

He was then referred to the department of cardiothoracic surgery. Since all sample cultures (sputum and bronchial lavage) remained sterile after 3 weeks, we performed lobectomy. He underwent a right pneumonectomy for the severe adhesion of the hilum (Fig. 4). Postoperatively we continued liposomal amphotericin B for 10 days. Intravenous insulin was continued to control blood glucose. He was discharged in good condition to the department of endocrinology, to control his diabetes mellitus. More than

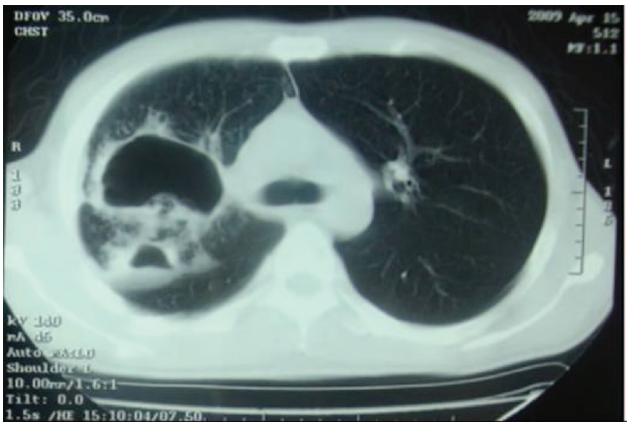

Fig. 1. Computed tomogram shows a cavitary consolidation in the right upper lung.

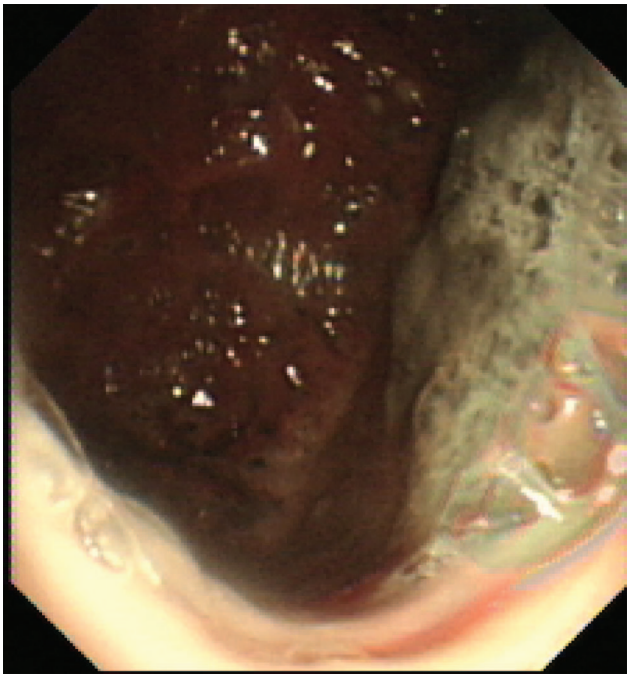

Fig. 2. Bronchoscopy shows a nodular growth completely obstructing a bronchi in the right upper lobe.

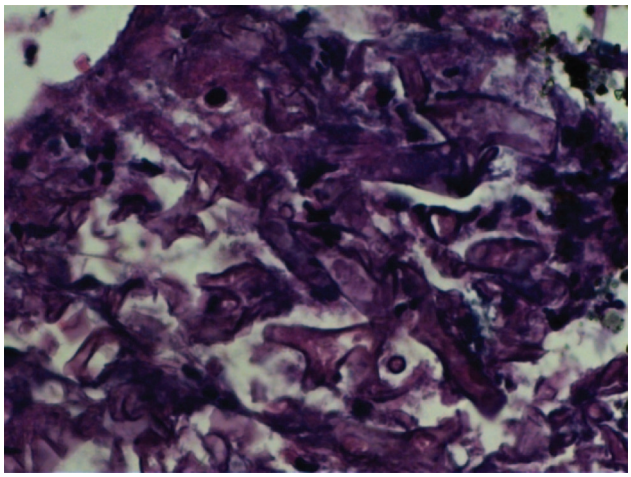

Fig. 3. Biopsy (hematoxylin and eosin stain), shows a broad organism with nonseptate hyphae.

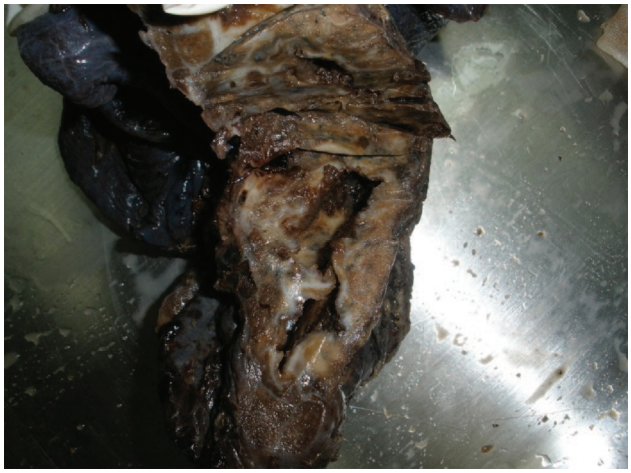

Fig. 4. Resected right lung shows characteristic features of zygomycosis, including angio-invasion and vascular thrombosis that cause characteristic blackening.

6 months after surgery the follow-up period was uneventful. He remains stable without any clinical or radiological evidence of recurrence, and is seen regularly in the thoracic surgery department and our department.

Discussion

The most common predisposing condition in patients with zygomycosis is diabetes mellitus: 50–75% of these patients have poorly controlled diabetes mellitus,[2] as in our patient. Various studies have shown that diabetes mellitus is one of the most important predisposing factors for pulmonary zygomycosis. Cancers, organ transplantation, burns, and malnutrition can also predispose patients to zygomycosis.[3-5] Diabetic patients are predisposed because of the decreased phagocytic function of their neutrophils, and the acidosis and hyperglycemia, which provide an excellent environment for the fungus. Hyperglycemia and acidosis in patients with diabetic ketoacidosis, and patients with severe burns, impair chemotaxis and oxidative fungicidal mechanisms in neutrophils. Serum from patients in ketoacidosis allows the replication of zygomycetes in vitro. Iron competition seems to be an important defense mechanism against zygomycetes. Also the iron-binding capacity of normal serum decreases in acidotic conditions and with glycosylation of transferrin, as happens in diabetic patients.[6] Patients on deferoxamine are particularly vulnerable to zygomycetes.

The symptoms of zygomycosis are highly variable and depend on the affected sites and the extent of the disease. A characteristic feature is angio-invasion and vascular thrombosis, which gives the lesions a characteristic blackened appearance on gross examination.[7]

Zygomycosis is usually confined to one lung segment, and through contiguous spread involves adjacent areas. As the infection causes angio-invasion and traverses through tissue planes, it may lead to cavitation and hemoptysis. The radiographic appearance of zygomycosis lung lesions is variable. Patients with diabetes are much more likely to develop endobronchial lesions.[8]

The clinical findings in zygomycosis are nonspecific, and it is crucial to have a high index of suspicion with susceptible patients. Tissue swabs and examination of specimens such as sputum, sinus secretions, and bronchoalveolar lavage fluid are usually nondiagnostic. However, when positive, they are usually a strong indicator of disease.[7] Tissue biopsy with histopathological examination is specific. The more usual radiographic findings of pulmonary zygomycosis range from normal, to lung abscess, to subacute or chronic pneumonia that often evolves into a lung abscess or to a rapidly progressive fatal pneumonia. The pulmonary form of zygomycosis is difficult to diagnose because of the nonspecific radiological findings and the usual necessity of an invasive approach and biopsy.[6]

An early multidisciplinary approach is critical for successful treatment of zygomycosis. It is necessary to reverse the predisposing condition whenever possible, to surgically debride devitalized tissue, and to administer appropriate antifungal therapy.[4] Resection of selected pulmonary and sinus lesions may be critical in optimizing outcome. Necrotic tissue may present a barrier to antimicrobial penetration, and even in cases where the mold is susceptible in vitro, therapy can be ineffective in vivo.

Combined surgical/medical treatment may provide better survival than medical therapy alone. In a review of 87 cases of pulmonary zygomycosis, mortality was lower with a combined surgical/medical approach, versus medical therapy alone (27% vs 55%).[8] In series of 255 patients from various studies, the mortality of patients treated surgically was 11%, compared to 68% in those treated medically ($P < .001$).[9] Urgent debridement of necrotic tissue is necessary, and frequently repeated debridement is required for disease control. The extent of debridement should be guided by frozen section.

Treatment with amphotericin B lipid formulations in combination with surgery, and perhaps the addition of caspofungin, offers the best chance for survival. Caspofungin is generally good at treating candida and aspergillus infection but is usually ineffective against zygomycosis.[10] However, caspofungin may be useful if the patient has both zygomycosis and candida or aspergillus. Mixed invasive fungal infections with zygomycetes and other molds are fairly common. One case series found that in 27 patients with invasive zygomycosis, 5 patients also had invasive aspergillus.[3] Posaconazole, a new antifungal triazole, is increasingly used for consolidation or maintenance therapy. Because of the poor prognosis of zygomycosis, particularly in immunocompromised cancer patients, adjunctive treatments such as hyperbaric oxygen therapy, immunomodulatory cytokines, and in vivo iron starvation continue to be explored.[11]

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