 Persistent cavitations in pulmonary mucormycosis after apparently successful amphotericin B

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Abstract

A 67-year-old diabetic man developed bilateral pulmonary mucormycosis (PM). After long-term treatment with amphotericin B (cumulative dose of 30.6 g), clinical resolution was obtained, but small radiographic cavitations persisted. A late relapse occurred and bilateral lobectomy led to a definitive cure. Amphotericin B is not able to penetrate properly into PM cavitations. We suggest that persistence of cavitations should lead to consideration of surgery, even after a good response to amphotericin B.

Keywords: Pulmonary mucormycosis; Diabetes; Cavitation; Amphotericin B; Surgery

1. Case report

A 67-year-old diabetic man presented with an acute onset of fever, malaise, right pleuritic chest pain, cough, hemoptysis and an alveolar infiltrate in upper right lobe. After 5 days of intravenous treatment with amoxicillin-clavulanic acid he was discharged with oral therapy without fever and only mild respiratory symptoms. No control chest X-ray was performed.

Ten days later he returned to the hospital with similar symptoms. Leukocyte count was 14,700/mm³, blood glucose was 621 mg/dl and \( \text{pO}_2 \) was 54 mmHg. A chest X-ray showed a huge cavitation with an air-fluid level in the upper right lobe and a new infiltrate in the upper left lobe. A computerized tomography (CT) scan confirmed a right cavitation of 12 cm and also a left cavitated pulmonary consolidation (Fig. 1). In a bronchoscopy we observed a dislodged apical right upper lobe bronchi with thickened and irregular mucosae. The bronchial aspirate and the bronchoalveolar lavage were negative for Gram and acid fast bacilli stains, and mycobacterial and fungal cultures. A transbronchial biopsy revealed bronchial mucosae with squamous metaplasia, necrosis and non-septated fungus structures suggesting pulmonary mucormycosis (PM).

Surgery was rejected because of a poor general clinical condition, bilateral disease and low pulmonary function tests (FEV1 1030 cm³ – 37% of predicted value) so treatment with 1 mg/kg/day of amphotericin B was started. In the seventh week, a switch to liposomal amphotericin B (Ambisome® 5 mg/kg/day) was performed because of renal function deterioration. After 95 days of treatment (cumulative dose: 15.6 g) left lung cavitations had disappeared and the one in the right lung was just 1 cm wide, although residual images could still be seen in both upper lobes (Fig. 2). A second bronchoscopy showed no alterations and new biopsies of both upper lobes were negative for Mucor so the patient was discharged with a prophylactic 100 mg twice a week dose of liposomal amphotericin B on an outpatient basis.

Nine days after discharge, cough, purulent sputum, hemoptysis, fever and chest pain reappeared and a small increase in the size of the right upper lobe cavitation was detected. With an improved pulmonary function (FEV1 2260 cm³), a right upper lobectomy was performed. To ensure total fungus elimination this anatomic approach was preferred over less aggressive surgeries. Histology of the surgical piece revealed a necrotic cavity with Mucor organisms in the surrounding parenchyma. A left upper lobectomy was performed 2 months later with similar findings. The patient was discharged after a cumulative dose of amphotericin B of 30.6 g (28.7 g liposomal). Three years...
after surgery, he is free of symptoms, pulmonary tests are good (FEV1 1510 cm$^3$) and there is no radiological evidence of relapse.

2. Discussion

Mucormycosis is a rare fungal infection that affects almost exclusively in immunocompromised patients. Pulmonary is the second most common involvement after rhinocerebral disease. Chest roentgenogram is abnormal in over 80% of the patients and cavitation is found in up to 40% [1]. Less than 50% of the patients is diagnosed pre-mortem, the mean interval from admission to diagnosis being 18 days [1]. Fungal cultures from clinical specimens are frequently negative and definitive diagnosis usually requires histologic demonstration of invasion of blood vessel walls, thrombosis and hemorrhagic infarction and identification of Mucor specimens. Prognosis is poor and overall mortality is high [2,3]. Around 30–40% of patients with PM are diabetic, but these patients have a lower mortality (60–65%) than those with underlying hematological malignancies (around 80%) [1]. Therapy is based in three approaches: rapid control of the patient’s underlying predisposing condition, antifungal therapy and surgical debridement.

Amphotericin B remains the mainstay for PM treatment but its use has been limited by frequent dose-related side effects. Optimal dose is not defined but a minimum of 6 weeks of treatment has been recommended. A complete response in patients with systemic fungal infections has been associated with a cumulative dose of 75 mg/kg [4]. The use of high doses of amphotericin B (defined as a cumulative dose of 30 mg/kg or a total dose of 2000 mg) has been correlated with a good prognosis but this correlation could simply be due to a longer survival [2].

Most authors recommend to associate surgery when possible to improve survival. In patients with localized disease treated surgically Tedder reported a significantly lower mortality than those treated medically (9.4 versus 50%). He recommends amphotericin B initially and consider surgical resection only if response in 48–72 h is not adequate, the patient is an appropriate surgical candidate and PM is localized [1]. Recently, Lee et al. [3] found similar differences in mortality (55 versus 27%) favoring surgery [3]. However, patients who undergo surgery are also those in the best general condition and with more limited fungal disease, which might influence survival [2,3].

Ringden et al. [5] found lung tissue concentrations of amphotericin B to be lower than those in other tissues, suggesting that pulmonary fungal infections may require higher dosage of amphotericin B. To our knowledge, this is one of the highest dose of liposomal amphotericin B administered to a single patient. Even with high tissue concentrations of amphotericin B, failures can occur in relation with strain susceptibility to the drug [5]. Although no susceptibility test was performed, the initial and sustained good response in our case makes this unlikely. A prolonged poor host immunocompetence status can also affect the course of disease but in this patient diabetes was rapidly controlled. Persistence of cavitation seems to be an important reason for relapse. Although some cases of persistent alterations in CT scan without evidence of long-term reactivation have been reported [6], most reports correlate persistence of radiographic abnormalities (especially cavitation and an air crescent sign) with mucormycosis proven in surgery [3]. These patients usually do not show clinical improvement. However, two cases have been reported of patients with good initial clinical response [5,6] but persistent radiographic alterations in which invasive mucormycosis was demonstrated in deferred surgery.

Our patient showed not only a clinical improvement but also an apparent complete sustained resolution. However, radiographic alterations including small cavities persisted and Mucor was finally found in the surgical pieces from both lungs. Some authors have questioned the ability of amphotericin B to penetrate infarcted tissue and abscess cavities [7,8]. These cavitations may act as an organism reservoir impeding a complete resolution despite a correct

Fig. 1. Initial thoracic CT scan showing a 12 cm wide cavitation in the upper right lobe and a rounded infiltrate in the upper left lobe with small cavitations.

Fig. 2. Posteroanterior chest roentgenogram showing residual lesions in both upper lobes after 95 days of treatment with amphotericin B (cumulative dose of 15.8 g) and apparent clinical resolution.
use of amphotericin B. In these cases, surgery seems to be the definitive therapeutic option.

In conclusion, very high doses of amphotericin B followed by a good clinical response may not be associated with definitive cure of PM. We suggest that surgery should be considered as soon as medical condition improves in all patients with PM successfully treated with amphotericin B when radiographic alterations (specially cavitations) persist.

References