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Case Report Open Access

Treatment of Cerebral Mucormycosis with Prolonged Liposomal Amphotericin B (>1000 days)

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Abstract

Mucormycosis is a rare but invasive and potentially lethal infection caused by ubiquitous fungi of the order Mucorales. The primary mode of infection is inhalation of fungal spores. Rhinocerebral and pulmonary infections are most common, however, other organ systems including the central nervous system can be affected, presumably by occult fungemia. We describe the prolonged treatment course (>1000 days) of a patient with cerebral mucormycosis using liposomal amphotericin B (LAMB). Two different attempts were made to replace LAMB with posaconazole, but each occasion resulted in therapeutic failure. This case represents the longest course of LAMB reported in the literature.

Keywords: Cerebral Mucormycosis; Amphotericin B; LAMB; Pulmonary infections

Introduction

Mucormycosis is a group of aggressive life-threatening infections caused by fungi belonging to the order Mucorales, which have emerged as increasingly important pathogens in the past decade [1]. Fungi of the Mucorales order are ubiquitous in the environment, but human infections are uncommon and opportunistic. This fungal infection is highly invasive and results in high mortality; the number of effective therapeutic modalities is limited. Amphotericin B, and more recently lipid formulations of amphotericin, are considered the treatments of choice for these infections, but their long term use is often limited due to their adverse effects. Particularly prominent side effects of amphotericin B deoxycholate include infusion related adverse reactions, electrolyte disturbances, and nephrotoxicity [2]. To this end, more amphotericin B-based preparations including a few lipid formulations such as liposomal and lipid complex preparations designed to reduce adverse effects have been introduced. The case described here represents a patient who developed cerebral mucormycosis and was treated with liposomal amphotericin B (LAMB) for nearly 3 years (>1000 days) with moderate adverse events (dose adjustments for increased serum creatinine); two attempts to use oral posaconazole monotherapy failed. To our knowledge, this is the longest course of any form of amphotericin B use reported.

Case report

A 51 year old man with severe chronic obstructive pulmonary disease (COPD) for many years was hospitalized with respiratory failure and probable sepsis. His initial treatment regimen consisted of mechanical ventilation, antibiotics and high dose steroids. His course was complicated by septic shock, gastrointestinal bleeding, acute respiratory distress syndrome, and acute kidney injury requiring a brief period of hemodialysis. His condition slowly improved, and steroids were discontinued on day 30 of hospitalization.

One week later, a gradual onset of right-sided hemiplegia and decrease in mental status were observed on physical exam. Subsequent MRI of the brain demonstrated two left parietal area ring enhancing lesions, measuring 1.3 × 1.3 cm and 2.0 × 1.8 cm, with surrounding edema, suggestive of an infectious process in the brain. Empiric broad spectrum antibiotics including voriconazole were initiated as well as high dose steroids for the edema. A brain biopsy was performed which revealed non-septate hyphae with right angle branching consistent with mucormycosis (Figure 1). Cultures failed to grow any fungal organisms. Serum galactomannan was not obtained. The patient's overall health condition was so poor that surgery was deemed out of the question.

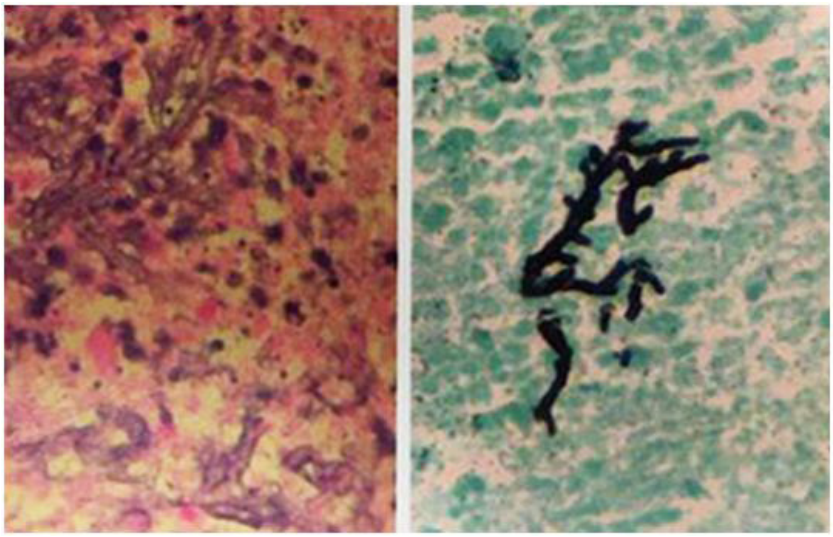
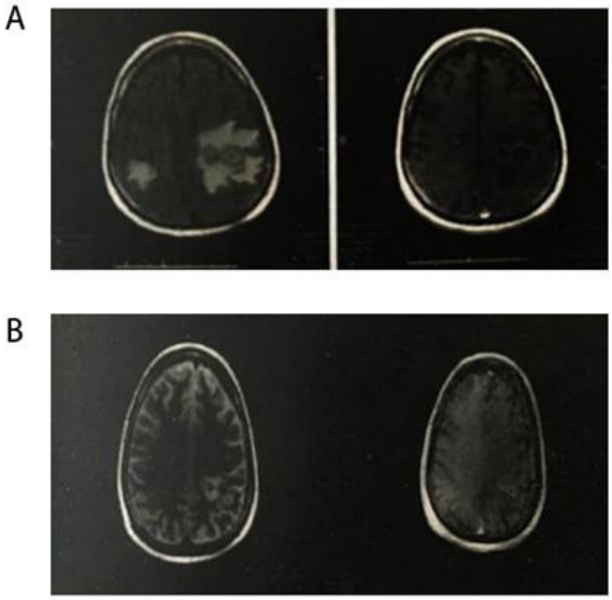


Figure 1: Photomicrograph of hematoxylin-eosin (H&E) and methenamine silver stain of brain biopsy revealing broad branching hyphae with characteristic right angle branching.

All antibacterials were stopped and voriconazole was changed to liposomal amphotericin B (LAMB) at 10 mg/kg/day. On day 9 of treatment, the patient was newly able to lift his right arm. On day 10, the dose of LAMB was decreased to 5 mg/kg /day, and oral posaconazole (400 mg orally twice daily with meals) was added. Repeat MRI of the brain on day 14 showed interval improvement of edema and, on day 28, further resolution of edema and a decrease in the size of the ring enhancing lesions. His strength continued to improve, and he was discharged home on this combination therapy.

Posaconazole was stopped on day 38 of treatment because of laboratory evidence of chemical hepatitis, and LAMB was continued. The hepatitis resolved and posaconazole was re-introduced on day 51 of treatment. Liver function was monitored and remained normal. He continued to show both clinical and radiologic improvement. We discontinued LAMB on day 166 of treatment, and he was continued on posaconazole monotherapy at 400 mg twice daily. On treatment day 221 he was admitted for bacterial pneumonia and repeat MRI of the brain showed slight enlargement of the left parietal lesions and a new contrast enhancing lesion in the right parietal lobe which extended to the meninges. Posaconazole was again stopped, and he was restarted on LAMB (5 mg/kg/day) on day 229 of treatment. On day 541, the patient developed acute kidney injury. Factors other than receipt of LAMB were likely contributory including dehydration and possibly other medications, but LAMB was discontinued and he was again switched to posaconazole monotherapy. On day 576, LAMB was resumed due to progression of his brain lesions on brain MRI. On day 704, the frequency of LAMB was reduced to thrice weekly from daily dosing due to an increase in his serum creatinine. On day 815, LAMB frequency was further reduced to twice weekly due to worsening renal function. He continued to receive LAMB, and tolerate it well, up to day 1088 when he died due to COPD-related respiratory failure. Serial MRI scan imaging studies are presented in (Figure 2).



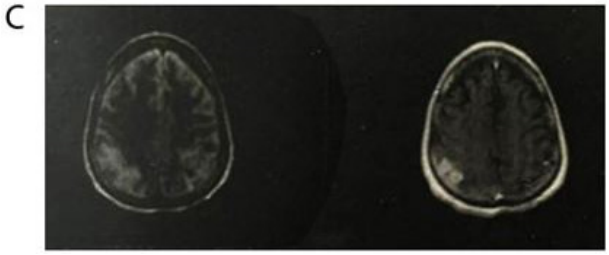


Figure 2: Serial MRI scan imaging of the brain, T2-weighted (left hand side) and T1 post contrast (right hand side): A, Day 1 of therapy with LAMB 10 mg/kg; B, Day 92 of therapy with LAMB (5 mg/kg) and posaconazole (400 mg orally twice daily); C, Day 228 of therapy (LAMB was stopped on day 166 and posaconazole monotherapy was substituted).

Discussion

Mucormycosis has emerged as an increasingly important fungal pathogen in the last decade [1,3]. Factors that have been associated with this phenomenon include the increase in patients with diabetes, an increase in hematopoietic stem cell transplantation, the use of voriconazole prophylaxis in patients at high risk for invasive fungal infection, and deferoxamine therapy [1,4,5]. In our patient, prolonged high dose steroid therapy for COPD-associated respiratory failure was most likely the major predisposition to invasive fungal infection, acutely impairing cell mediated immunity. The treatment options for mucormycosis are limited and the overall prognosis is poor. Localized CNS infection is an uncommon presentation of mucormycosis accounting for about 5% of all cases of mucormycosis; it is associated with a high mortality rate [1]. The treatment strategy in mucormycosis is based on limited clinical data and expert opinion. The basic treatment principles intended to increase the chances of cure are early diagnosis, reversing or minimizing predisposing factors, surgical debridement (if possible), and early antifungal therapy [6,7]. In our patient, the inability to perform surgery likely contributed to his need for such prolonged LAMB therapy.

Amphotericin B deoxycholate is the backbone antifungal agent in the management mucormycosis, its use mainly being limited due to its toxicities [8]. The lipid formulations of amphotericin B are considered to be a superior option primarily because of their favorable toxicity profile compared to amphotericin B deoxycholate. The largest comparative trial to date, which involved 687 patients, showed renal toxicity in 19% in the LAMB arm compared to 34% in the amphotericin B deoxycholate arm. No difference in efficacy was shown [9]. This toxicity advantage has been demonstrated in multiple randomized prospective studies which have consistently shown LAMB to be less nephrotoxic than amphotericin B deoxycholate [1]. There is evidence that LAMB, compared to the other lipid formulated amphotericin B preparations, achieves higher concentrations in the brain [12].

The optimal cumulative dose of LAMB needed to cure CNS mucormycosis is not known due to paucity of clinical data. Commonly used daily doses fall in the range of 5~7.5 mg/kg/day. However, doses of 10 mg/kg/day have been suggested due to the limited polyene penetration into the brain, though little data support this dosing strategy [7]. This theoretical benefit, must be weighed against data showing that higher doses have greater toxicity. One study of treatment of invasive mold infection randomized patients to LAMB 10 mg/kg/day and compared it to 3 mg/kg/day for 14 days. No difference in clinical outcomes was observed. More patients in the high dose group than the low dose group had to discontinue LAMB (50% vs 34%; p=0.04) mainly due to nephrotoxicity and hypokalemia [11]. Of note, greater than 95% of patients in this study had pulmonary aspergillosis.

Despite being on LAMB for nearly 3 years, our patient tolerated the regimen well with only moderate nephrotoxicity but without necessitating a change in therapeutic modality. After about 2 years, we increased the dosing interval of his LAMB regimen because of a slow decline in his kidney function. We also instructed his caregiver to give him intravenous normal saline prior to infusing LAMB. This may have helped to minimize the nephrotoxic effects of the drug.

Posaconazole is an extended spectrum triazole that has shown activity against mucormycosis in vitro, and it has been used in patients as salvage therapy [13,14]. In one case series, posaconazole showed a success rate of 72.6% when used as salvage therapy for patients with cerebral mucormycosis. The study was limited by small sample size; there were only 11 cases of cerebral mucormycosis and patients were followed for only 12 weeks [14]. Still, these data suggest that oral posaconazole may have activity against cerebral mucormycosis. In our patient, however, oral posaconazole monotherapy was attempted twice without success, evidenced by progression of brain lesions on MRI.

Our patient demonstrated the many management challenges inherent in the treatment of cerebral mucormycosis. Overall we were successful in controlling this infection by continuing LAMB for almost 3 years. Somewhat to our surprise, the patient tolerated LAMB well and did not develop any major toxicity during the majority of his treatment course. In conclusion, prolonged LAMB therapy may successfully suppress cerebral Mucormycosis in selected patients who might otherwise succumb to this difficult to treat infection.

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