CASE REPORT

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Liposomal amphotericin B treatment for rhinocerebral mucormycosis: How much is enough?*

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SUMMARY

Rhinocerebral Mucormycosis is a potentially life-threatening disease, which affects mainly immunocompromised patients. Treatment options include reversing immunosupression, surgery and systemic and local administration of anti-fungal medication. Amphotericin B is the primary agent employed, but its use is often limited by frequent side effects. Complexing Amphotericin B with lipid structures avoids most of the negative side effects, most importantly the dose-limiting nephrotoxicity. No consensus has been reached regarding the appropriate duration, rate of administration or total dose of treatment.

We present a case of a patient suffering from Rhinocerebral Mucormycosis treated by extensive surgery and Liposomal Amphotericin B. He was treated for 29 days at a rate of 3 mg/kg/d and a total dose of 5.6 gram. The dose of Liposomal Aphotericin B used in previously published articles ranged from 1.5 mg/kg/d to 5 mg/kg/d. The response to treatment may be evaluated by physical examination, microbiological cultures, radiological and pathological studies. Taking into account the considerable cost of liposomal Amphotericin B and other lipid complexed formulations, it is imperative to find out what is the appropriate treatment regime for Rhinocerebral and other mucormycosis infections.

Key words: paranasal sinuses, mucormycosis, Amphotericin B, lipid-complexed

INTRODUCTION

Invasive Mucormycosis is a life-threatening disease, mainly affecting the immunocompromised patients. Treatment options include reversing immunosupression whenever possible, surgery and systemic and local anti-fungal medications. Amphotericin B is the primary agent employed, but its use is often limited by side effects. Complexing Amphotericin B with lipid structures avoids most of the side effects including the dose-limiting nephrotoxicity (Luke and Boyle, 1998; Walsh et al., 1999). The criteria for the eligibility of patients for this expensive treatment have been suggested (Walsh et al., 1998), but no consensus has been reached regarding the appropriate duration, rate of administration and total dosage of treatment. Following, we present a case of invasive mucormycosis of the para-nasal sinuses treated by liposomal Amphotericin B and address the clinical questions raised in this setting with special emphasis on the duration and total dose of treatment required.

PATIENT'S REPORT

A 75-years old male presented with a ten-week history of right cheek swelling. Past medical history included diet controlled Type II Diabetes Mellitus. His current disease appeared during an exacerbation of chronic obstructive pulmonary disease treated with low dose systemic corticosteroids.

Physical examination revealed mild swelling of the right cheek up to the zygoma, mild exophthalmus and no pathological tissue in the nasal cavity. Upper jaw dentures were mispositioned but otherwise examination of the oral cavity and pharynx was normal. The patient was aprexic. Cranial nerves were intact.

CAT scan demonstrated maxillary sinuses filed with tissue of medium density. Destruction of the bony lateral wall of the right maxillary sinus and the orbital floor was observed (Figure 1).

In order to acquire tissue for diagnosis, he was operated on. The maxilla was found to be necrotic. Primary pathological impression was Aspergillus and treatment with deoxycholate Amphotericin B (dose 0.7 mg/kg/d) was initiated. Following, total maxillectomy and right zygomectomy were performed as these bones were found to be necrotic. The soft palate was retained. The final pathological examination and fungal culture confirmed the diagnosis of infection with Mucormycosis (Figure 2).

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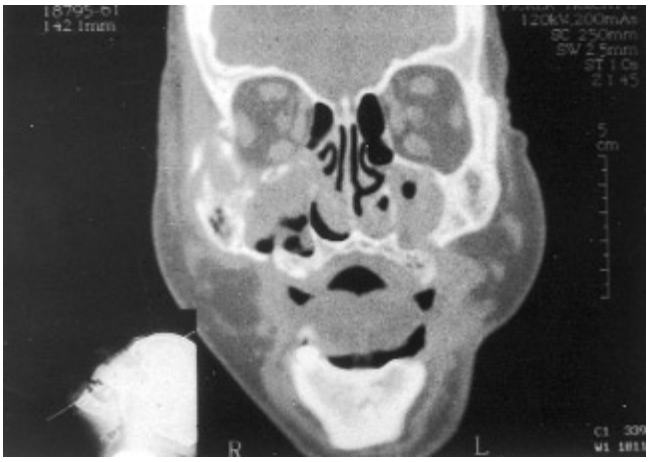

Figure 1. Coronal CT scan illustrating extent of bone destruction of the right orbital floor, the floor, medial and lateral right maxillary sinus walls, and floor of the left maxillary sinus.

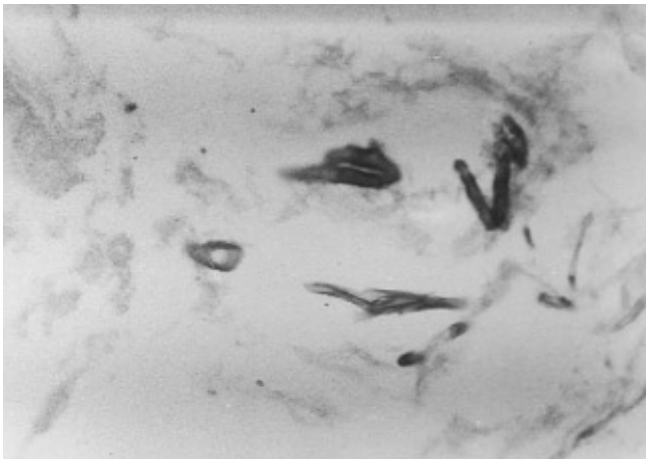

Figure 2. Histological slide with Pas stain -A fungi with wide hypha, irregular branching compatible with *Mucormycosis* is demonstrated. In contrast to *Aspergillosis*, no septa are seen.

After five days of treatment the patient suffered from acute renal failure as manifested by his creatinine level rising from 1 mg/dL to 3.5 mg/dL. Treatment was changed to infusion of liposomal Amphotericin B (AmBisome, NeXstar, Boulder, CO, USA) at a dose of 3 mg/kg/d.

The patient received 29 days of therapy with a total dose of 5.6 grams. This relatively high dose of AmBisome was selected due to the extent of the infectious involvement and the eminent danger of intracranial and intraorbital penetration. Utilising the large bony defect left after surgery, decision to stop the antifungal treatment was based upon physical examination aided by biopsies and cultures. With this treatment his creatinine level stabilised around 2mg/dL. Fifteen months after surgery the patient is free of disease and with an obturator enjoys full oral functions.

DISCUSSION

Rhinocerebral mucormycosis is the most common clinical form of mucormycosis. The invasive nature of the pathogen, the proximity of the infectious process to the orbit and intracranial structures and immunodeficiency of the host, all combine to make this entity a debilitating and often lethal disease.

Correction of immunosupression whenever possible is crucial to the success of treatment. Surgery has a definite role for removing all devitalised tissue, at times requiring extensive procedures. In suitable cases anti-fungal treatment can be started before surgery as a mean to restrict the area in need for débridement.

Raj et al. (1998) recommended adding inhaled Amphotericin B for rhinocerebral mucormycosis as a measure to elevate the level of the drug in its target region without significantly altering serum levels of the drug. Hyperbaric oxygen is another suggested adjunctive measure, as a method to improve tissue oxygenation, neutrophil oxydative potential and to lower the acidity at the infection site (Couch et al., 1998).

The treatment of choice is systemic Amphotericin B. As gastrointestinal absorption of the drug is negligible, parental administration is required. Unfortunately, use of this agent is often limited because of frequent severe side effects, primarily renal failure. To help minimise the toxicity of deoxycholate Amphotericin B, liposomal and other lipid complexed versions have been developed. Previously published literature elaborates the mechanism of action of this new class of drugs (Heimenz and Walsh, 1996; Boswell et al., 1998). Liposomal Amphotericin B has a highly elevated therapeutic index, most likely due to its uptake by macrophages. These cells deliver the drug-lipid complex to the site of infection bypassing uninvolved tissues such as the kidneys. The drug containing spheres are subsequently disrupted mainly after attachment to the fungal cell wall, thereby releasing the drug into the fungal cells. Tissue concentration of liposomal Amphotericin B therefore varies significantly between different body organs, being lower in kidneys and higher in the macrophage rich reticular-endothelial cells (Boswell et al., 1998).

Indications for the treatment by liposomal Amphotericin B are intolerance to Amphotericin B deoxycholate, previous renal failure and non-responding patients (Heimenz and Walsh, 1996). Continuation of Amphotericin B deoxycholate treatment in the face of deterioration of renal function may result in permanent renal failure. Underlying medical conditions such as diabetes mellitus or concurrent viral or bacterial infections are common risk factors for renal failure. Treating rhinocerebral mucormycosis with liposomal and other lipid-complexed Amphotericin B has been reported on a case report basis (Strasser et al., 1996; Couch et al. 1998).

As the infected area is typically poorly vascularized and considering the fact that most affected patients are immunosuppressed, relatively long courses of treatment are required. The

overall length and total dose of treatment with antifungal agents are not well established, and left to the physician's clinical judgement. Published case reports differ widely in terms of daily and total dose of the drug administered and length of treatment, at least partly due to differences in the extent of the infection and the general condition of the patients.

In one instance the decision to halt the treatment was based upon CT imaging and negative biopsies from the site of infection after a total dose of 25 grams of Amphotericin B lipid complex (Liposome Co. Inc., Princeton, NJ, USA) infused for 18 months at the rate of 5 mg/kg per day, first daily and later at growing intervals (Strasser et al., 1996). On the other hand, lower doses and shorter courses are reported. Lim et al. (1994) used a dose of 1.5 mg/kg/d, and similar doses were used earlier by Fisher et al. (1991).

Raj et al. (1998) reported a course of six weeks of treatment with liposomal Amphotericin B at 1 mg/kg/d increased to 3 mg/kg/d. At the end of this course and based on abnormal CT findings the patient underwent an operation and diseased tissue removed with no further anti-fungal therapy.

The FDA approved dose of liposomal Amphotericin B for empirical use in neutrophenic patient is 3 mg/kg/d. For patients suffering from cryptococcus, candidiasis or aspergillus the dose is 3 to 5 mg/kg/d (Mandell, 2000). Liposomal Amphotericin B has proved to be at least as effective as Amphotericin B deocycholate in the empirical treatment of patients with fever and neutropenia, and with less side effects (Walsh, 1999). A large study comparing 1 mg/kg/d to 4 mg/kg/d of Liposomal Amphotericin B in 87 patients suffering from invasive Apergillosis found no significant difference between the efficacy of the two doses (Ellis, 1998).

It appears that the extensive resection needed in the presented case and others was beneficial in allowing the direct and endoscopic examination of all of the infected area. When possible, physical examination supported by cultures and biopsies of suspicious findings may be a more accurate tool than imaging for the evaluation of response to treatment and the decision to end anti-fungal treatment. Reconstructive efforts must take into account the importance of direct surveillance of the surgical field as an important tool for the decision to stop the treatment with Amphotericin B. Thus, for rhinocerebral mucormycosis especially if originating from the maxillary sinuses, removable obturators may be the proper initial reconstruction method.

Taking into account the considerable financial burden of the treatment with liposomal amphotericin B (about 60 fold compared to Amphotericin B deoxycholate (Mandell, 2000)), it can be beneficial to find out what is the lowest dose and shortest course required for effective treatment. This question is relevant not only to the rhinocerebral disease but to other clinical forms of infection by mucormycosis as well, and other fungal infection, which are treated by liposomal and other lipid-complexed Amphotericin B.

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