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ORIGINAL ARTICLE

Amphotericin B Emulsion in Rhino-orbital Mucormycosis: Is It Most Effective?

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ABSTRACT

Mucormycosis is a fatal infection of the immunocompromised individuals. It is unusual to affect healthy individuals. The main aim of this case report is to highlight the role of amphotericin B emulsion in this disease. The case was managed in our set-up with surgical debridement and followed by amphotericin B emulsion for 4 weeks. We did not notice hypokalemia and renal function test abnormality in the entire course of the treatment. We present the case and the review of the literature of newer lipid complex amphotericin.

Keywords: Amphotericin, Mucormycosis, Rhino-orbital.

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INTRODUCTION

Mucormycosis, also known as zygomycosis and phycomycosis, was first described by Paultauf in 1885.[1] It is caused by fungi that are commonly found in soil and among decaying vegetation. It is an aggressive and often fatal disease that occurs mainly in people with immune disorders, such as uncontrolled diabetes, malnourishment, and severe burns.[2-4] It involves the rhino-facial, cranial area, lungs, gastrointestinal tract, skin, and less commonly other organs, but can also present as a disseminated disease. Secondary infections are common and the course of the disease is typically fulminant.

Mucormycosis is a fatal, rapidly destructive, opportunistic infection, often seen in immunocompromised individuals. It is caused by fungi, of the order Mucorales, family Mucoraceae,[5] which include the genera Absidia, Mucor, Rhizopus, Rhizomucor, and Cunninghamella. These are ubiquitous in nature, and humans usually have a strong natural resistance to infection. However, in association with diabetic ketoacidosis or other chronic debilitating disorders, the organisms may become pathogenic. Treatment is by surgical removal of all necrotic tissue along with intravenous antifungal agents and control of the original precipitating cause. There is a high mortality (25–80%) even after this aggressive approach.[6]

CASE REPORT

A 42-year-old male presented to the ear, nose, and throat (ENT) emergency with protrusion of the left eye ball, loss of vision in left eye, and headache since 10 days (Fig. 1). The patient was admitted to the ENT ward on an emergency basis, and thorough history taking, meticulous clinical examination, and routine hematological and biochemical investigations were done in all the patients. On anterior rhinoscopy, there was blackish discoloration in the left nasal cavity and the presence of crusts. Nasal endoscopy was performed and tissue sample sent for fungal smear on KOH mount; the report showed aseptate hyphae. Blood sugar was 450 mg% on admission and there was no ketone body in urine. The patient was subjected to computed tomography (CT) scan and magnetic resonance imaging (MRI) (Fig. 2). The noncontrast CT scan of paranasal sinus revealed there was soft tissue density in

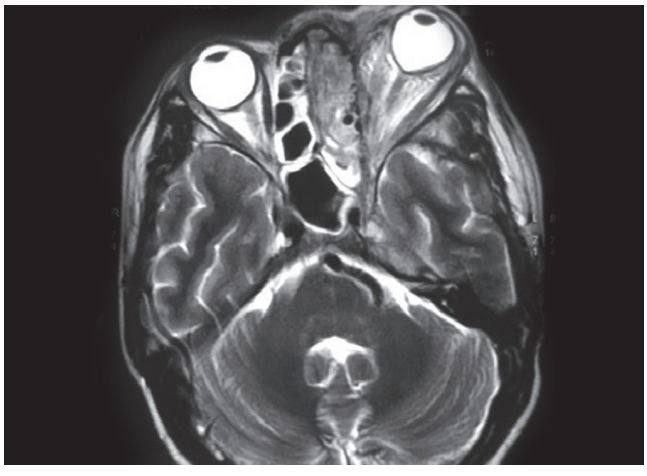

Fig. 1: MRI PNS and orbit showing lesion in PNS and orbit

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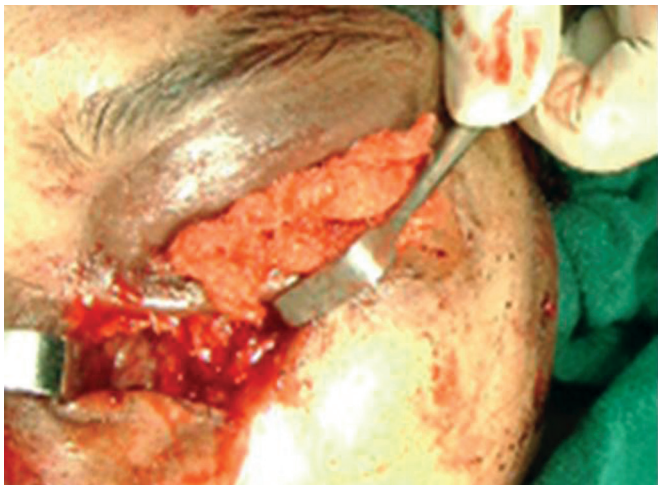

Fig. 2: Intraoperative image

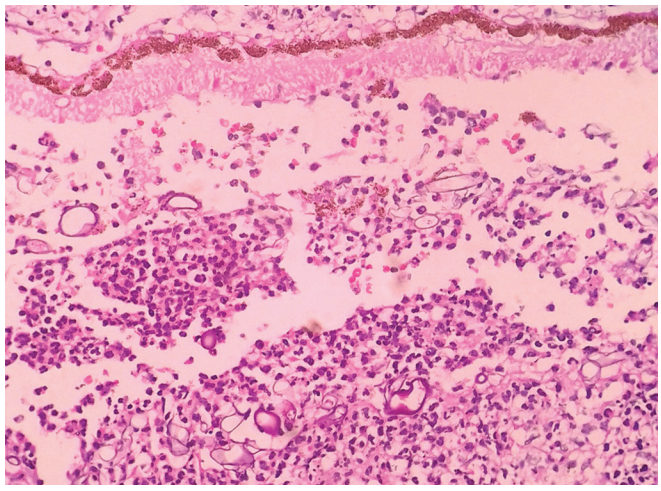

Fig. 3: HPE showing aseptate hyphae

the left maxillary sinus and orbit. The MRI of the brain showed there was frontal lobe abscess. After neurology and neurosurgery consultation, debridement with left orbital exenteration was done (Fig. 3). The histopathology of the specimen reveled mucormycosis. The patient was given amphotericin B emulsion at 3 mg/kg body weight for 28 days. The amphotericin B chart was maintained for electrolytes, blood sugar, and hemoglobin. During this period we observed initial hypernatremia and subsequently the mean serum potassium was 3.94 ± 0.83 [± 2 standard deviation (SD)]. The mean value of serum urea was 1.13 ± 0.09 (± 2 SD) and that of serum creatinine was 42.56 ± 8.18 (± 2 SD).

DISCUSSION

Mucormycosis attacks people with compromised immune systems. Reduced ability of the serum to bind iron at low pH may be the basic defect in the body defense system.[7] Human resistance to fungal infection rests on the ability to restrict the availability of iron to the invading fungus by binding it to proteins, such as Apo transferrin. Fungal hyphae produce a substance called rhizoferrin, which binds iron avidly. This iron–rhizoferrin complex is then taken up by the fungus and becomes available for vital intracellular processes. Phycomycetes can grow fast, and mucormycosis can destroy the sinuses within a day and invade the brain of a susceptible person.[8]

Diabetes mellitus, particularly when it is poorly controlled and causes acidosis, is a risk factor as it relates to cellular immune dysfunction. In two of the patients who survived, there was complete loss of the tissues of the cheek on the involved side including the skin, soft tissues, maxillary antrum, palate, and orbital contents. In these two patients, we used bipedal pedicled pectoralis major myocutaneous flaps to repair the defect.

Mucormycosis is a medical emergency. Proper management of a patient with mucormycosis centers on early recognition of symptoms and initiation of vigorous surgical and medical therapy. Regulating diabetes and altering the dose of immunosuppressive drugs aid in the treatment and greatly improve survival. Amphotericin B is the antifungal agent of choice. It is a polyene antimicrobial that acts by binding to sterols (primarily ergosterol) in the fungal cell membrane with a resultant change in membrane permeability. Amphotericin B is highly protein bound (90%) and poorly dialyzable. After intravenous administration, approximately 66% of plasma concentrations have been detected in the aqueous humor. Concentrations in the cerebral spinal fluid seldom exceed 2.5% of those in the plasma; little amphotericin B penetrates into the vitreous humor. Initially a test dose of 1 mg in 20 ml of dextrose 5% in water is infused intravenously over 20 to 30 minutes, with careful monitoring for side effects (i.e., chills, fever, phlebitis, renal damage, and anaphylaxis) every 30 minutes for 2 to 4 hours. If this dose is well tolerated, an initial dose of 0.25 to 0.3 mg/kg/day is then prepared as a 0.1 mg/ml infusion and delivered slowly over 2 to 6 hours. Depending on the patient's cardiorenal status, the dosage may be gradually increased by 5 to 10 mg/day, up to a total dose of 0.5 to 0.7 mg/kg/day. If minor side effects occur, the maintenance dose can be doubled and given on alternate days, but a single dose should not exceed 1.5 mg/kg; overdoses can result in cardiorespiratory arrest.[9]

Lipid complex amphotericin B is a formulation designed to be less nephrotoxic than conventional amphotericin B. This lipid-based formulation increases the circulation time and alters the biodistribution of the associated amphotericin B. Because drugs complexed with lipid vehicles have a longer residence time in the vasculature, they are able to localize and reach greater

concentrations in tissues with increased capillary permeability (i.e., infection and inflammation) compared with regions of normal tissue, which are essentially impermeable to lipid–complex drugs. This method of increasing the localization of drugs to diseased sites is referred to as passive targeting. It enhances delivery of the agent to the fungi, infected organs, and phagocytes with lower toxicity, while maintaining antifungal efficacy through significantly higher sustained tissue levels of the drug. Within these sites, drug release occurs through the action of lipases from surrounding inflammatory cells.[10,11] The lipid formulations also may enable better solubility into the central nervous system. The cerebrospinal fluid penetration of conventional amphotericin B is known to be poor, and although the concentration of lipid-based amphotericin B in brain tissue remains unknown, studies describe its successful use in cryptococcal meningitis.[11] Furthermore, the lethal dose (LD50) of lipid-based amphotericin B is approximately 10 to 15 times higher than that of conventional amphotericin B, with substantially reduced renal toxicity.[10] Thus, the lipid formulations are ideally suited for therapy against infections, such as rhinocerebral mucormycosis, which require large doses of drug given for long periods of time. The recommended dose of liposomal amphotericin B is 5 mg/kg/day prepared as a 1 mg/ml infusion and delivered at a rate of 2.5 mg/kg/hour.

In our case we had normal serum potassium during the entire course of treatment and also the frontal lobe abscess was resolved with 3 mg/kg/day. This is a new added fact to the literature that amphotericin B emulsion does not cause hypokalemia and renal function test abnormalities in this case.

Hyperbaric oxygen has been used as an adjunct to aggressive surgical debridement, amphotericin B therapy, and control of any underlying predisposing conditions. Although studies have shown that hyperbaric oxygen exerts a fungi static effect, the most important effect of hyperbaric oxygen is to aid neovascularization, with subsequent healing in poorly perfused acidotic and hypoxic but viable areas of tissue. Tissue changes caused by microvascular insufficiency secondary to obliterative arteritis occurring after radiotherapy are similar to the changes seen with the vascular occlusion by mucormycosis, as well as other fungal infections. Hyperbaric oxygen therapy for mucormycosis should consist of exposure to 100% oxygen for 90 minutes to 2 hours at pressures from 2.0 to 2.5 atmospheres with one or two exposures daily for a total of 40 treatments.[12,13]

The management of this disease demands a multidisciplinary approach. The normal serum potassium, normal serum urea, and creatinine and the efficacy of this drug at 3 mg/kg/day need to be studied in large-scale trials.

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