Mucormycosis - Dual Therapy with Prolonged Survival

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Abstract

Mucorales fungal infection is a fungal disease with potentially fatal outcomes. The most frequent involvement in humans comes from the orders known as Mucorales and Entomophthorales. Mucorales is more acute and has a predilection for immunocompromised patients. Mucorales are associated with an affinity for vessels, which leads to invasion and infarction of tissue. Mucormycosis is a devastating complication that can be a life threatening fungal invasion in many patients in an immunocompromised state.

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Case Presentation

In 2014, a 69-year-old Panamanian female with a past medical history of diabetes mellitus type 2 and the presence of a pterygium on her conjunctiva had had resection a month prior of her pterygium and placement of an amniotic membrane graft to her left eye for which she had been treated with longterm corticosteroids. She presented to the emergency department of a hospital in Panama City, Panama with a history of one week of evolution of swelling of the right side of her face, ipsilateral eye proptosis and odynophagia. A large ulcer (3 X 4 cm) in her hard palate was evident.

Her labs showed anemia (hematocrit 27%), leukocytosis (15,000 cells/mL³), neutrophilia (73%), acute kidney injury (creatinine 2.0 mg/dL) and diabetic ketoacidosis with an elevated anion gap of 16 meq/L. As part of the emergency diagnostic approach, she had a nasal endoscopy during which they observed a necrotic lesion in the septum with cotton-like texture at the level of the nostrils. (Video 1)

The CT scan revealed inflammatory changes, a fluid collection and inflammatory necrotic tissue in the masticatory space that extended on the right to the pterygopalatine fossa and orbital apex (Figure 1). There was involvement (anterior to posterior) of her right eye (proptosis), compromise of intra- and extra-conal fat, the medial rectus muscle, and the superior orbital fissure, as well as asymmetry of the right cavernous sinus.

Video 1 Nasal endoscopic view of each nostril and a hard palate ulcer with necrotic tissue in a patient with Mucormycosis.

Figure 1 CT head scan with inflammatory necrotic tissue in the masticatory space that extended to the pterygopalatine fossa and the orbital apex. Post-surgical inflammatory changes are visible (large single arrow) as well as invasion of infection into the right carotid artery (line with two arrowheads).

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Figure 2
(A) Periodic acid Schiff stain (PAS) of necrotic nasal tissue showing a vessel with fungal invasion
(B) Enhancement of necrotic nasal tissue structures showing mucormycosis with silver staining (Gomori)

She was taken to the operating room three times for debridement and cleaning of necrotic tissue. The orbit decompression was draining pus. An open approach was performed including a subtotal maxilectomy (palate/pterygoid lamina). It was closed with a gingival flap of the oral palate. A tissue sample was taken to the pathology department where it showed tubular structures compatible with a fungus. Gomori stains and periodic acid-Schiff stain findings were consistent with mucormycosis (**Figure 2**).

Treatment included initially caspofungin alone without improvement, then amphotericin B deoxycholate was added as salvage therapy. Amphotericin B was given at a dose of 50mg daily (1 mg/kg/day) until a total cumulative dose of 2580 mg was given. Complications related to the medication were seen, especially nephrotoxicity due to the amphotericin B, therefore it was reduced to 30 mg/day (0.6 mg/kg/day).

After five months of dual antifungal therapy and multiple debridements, risk factors related to comorbidities continued to play an important role for lack of control of the disease. Poor glycemic control at home, nephrotoxicity and electrolyte disturbances complicated the outcome. She returned with a probable cerebral vascular event secondary to extension of the mucormycosis to the brain and died a week later.

Discussion

Rhinocerebral mucormycosis is a devastating infection with high mortality of 35% for patients with no underlying condition [1]. Its relationship with immunosuppression makes treatment of this fungal infection difficult. The most frequent involvement in humans comes from the orders known as Mucorales and Entomophthorales [2]. Infections usually begin in the paranasal sinuses following inhalation of sporangiospores and may involve the orbit, palate, face, nose or brain [2]. The important characteristic for the diagnosis of this disease is the vascular invasion and tissue necrosis similar to what we observed in the pathology of our patient, with wide hyphae (10-20µm), and right-angled branching without septa.

Entomophthorales in the tropics are associated with chronic conditions of the skin and subcutaneous tissue [2]. Mucorales has an affinity for vessels and leads to invasion and infarction of tissue [3]. Mucor species are typically avirulent due to a lack of thermo-tolerability in the presence of a healthy host immune system, but will manifest with disease in the presence of immunosuppression[4]. Rhizopus orizae is the most common isolated filamentous fungus from patients with mucormycosis

causing at least 90% of cases related to rhinocerebral mucormycosis [1]. Mucormycosis appears as an opportunistic disease due to certain risk factors (**Table 1**). The number of patients with predisposing risk factors has increased making the disease more prevalent. The overall mortality rate for a diabetic patient is as high as 44% [2]. Our patient's main comorbidity was the decompensation of her diabetes, which accounted for her predisposition to, and the persistence of, her infection.

Prevention of mucormycosis can be attained with control of diabetes mellitus by maintaining normal glycemia levels, correcting ketoacidosis, and avoiding corticosteroid therapy. Proper treatment with a favorable outcome depends on both medical treatment and good initial debridement.

Mucormycosis invasiveness may be based on the availability of iron in serum and tissue [5]. Iron will promote neurotropism and invasion. The low pH in uncontrolled diabetes also decreases the activity of transferrin, which results in more free iron in the blood for Mucorales [6]. The rhinocerebral, pulmonary and disseminated presentation of mucormycosis all have necrosis, thrombosis and invasion of blood vessels in common [5]. 1,3-β-D-glucan detection is not useful in this kind of infection due to extremely low content of this molecule in Mucorales [5,7].

It is well known that macrophages and neutrophils have an important role in immune defense. The functional defects caused by therapeutic interventions such as corticosteroids play a crucial risk factor for Mucorales to infect [5]. Diabetes alone can impair the function of neutrophils contributing to the severity of mucormycosis in patients with ketoacidosis [8]. Macrophages have a diminished phagocytotic effect and neutrophils have a diminished chemotactic and oxidative burst due to the low pH during ketoacidosis [6].

Table 1 Risk factors for acquiring mucormycosis.

Risk Factors for Acquiring Mucormycosis
Immunosuppression
Neutropenia
Corticosteroid therapy
HIV infection
Organ transplant
Uncontrolled Diabetes/Diabetic ketoacidosis
Chronic metabolic acidosis
Treatment with deferoxamine

One study found that the host receptor, glucose regulated protein (GPR78), facilitates the invasion of human endothelial cells by *R. oryzae* due to the presence of high iron and glucose concentrations [9]. In the diabetic murine model, there was a direct relationship between an increased expression of this protein and the damage of endothelial cells [9].

This is a disease condition without many therapeutic options due to the severity of disease. The standard treatment recommended in rhinocerebral mucormycosis is amphotericin B with debridement, but the combined treatment of amphotericin B plus either an echinocandin or an azole with debridement was shown to improve survival in three cases [10,11]. Drugs that have an FDA approved indication for mucormycosis are amphotericin B with its lipid derivatives, and isavuconazonium sulfate, the pro-drug of isavuconazole, which was not available until 2015 (a year after this patient's death).

The genome sequence of *R. oryzae* has led to the discovery of genes involved in ergosterol biosynthesis and two genes that code for 1,3- β -D-glucan synthase [12]. These findings help us understand why there is evidence that caspofungin inhibits glucan synthase activity of *R. oryzae*. 1,3- β -D-glucan is a small part of the Mucorales cell wall and echinocandins are the only antifungal to target the cell wall – most target the cell membrane. Thus, echinocandins, may be considered during failure as an additional component of salvage therapy [12].

This patient was offered a combination of amphotericin B deoxycholate plus caspofungin based on studies of rescue therapy [13] as a last measure. However, she ultimately died due to the mold infection. From the time of her diagnosis, she lived approximately six months.

Rhinocerebral mucormycosis is invasive and carries a poor prognosis. Diabetes mellitus is a major risk factor and its incidence is increasing globally, so patients presenting with uncontrolled diabetes should be investigated for possible mucormycosis. There is not a specific treatment duration. It depends on clinical evaluation of the affected area and the presence of the healing process after multiple debridements. Amphotericin B or isavuconazonium sulfate is good initial treatment if it is combined with surgical removal of necrotic tissue. Combined therapy with an echinocandin may be an efficacious and less toxic alternative for maintenance therapy.

Infections with Mucorales are present worldwide. It has been well documented in Europe, India, Japan and the United States [3,6,14,15]. More recent documentation of cases has come from Burkina Faso, Iran and Taiwan [16-18]. There has been a documented predilection for mucormycosis from August to October/November. One study was from Japan, which has its typhoon season at that time, but Iran and Israel, with more arid climates, also found a higher incidence during that time period [17,19,20]. As communities in the US become increasingly international, diabetes becomes more prevalent and solid organ transplants are performed more frequently, it is important to recognize the need to expand the differential diagnoses to include mucormycosis, accordingly.

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