Rhino-orbito Cerebral Mucormycosis in an Otherwise Healthy Patient with No History of Systemic Disease: A Case Report and Review of Literature

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Abstract

**Objective:** Rhino-orbito-cerebral mucormycosis is a rare invasive fungal disease, which often has a fulminant and characteristic clinical course. The patients are usually immune-compromised, with diabetic ketoacidosis. The underlying disease is an important factor determining the prognosis of infection and response to treatment.

**Case:** The authors report a case of fulminant rhino-orbito-cerebral mucormycosis with no apparent underlying disease. Therapy included surgical intervention and systemic administration of amphotericin B. However, due to the aggressive behavior of disease and occult underlying systemic condition the treatment was unsuccessful and the patient died after debridement and medical therapy.

**Conclusion:** Only a few cases of Rhino-orbito-cerebral Mucormycosis have been reported in the literature with no identified predisposing factor. In our case, no specific predisposing factors were found accompanying the fulminant progression of rhino-orbito-cerebral mucomycosis.

**Key words:** Mucormycosis, Rhinocerebral, Fungal

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Introduction:

Mucormycosis has been designated as the most fatal fungal infection known to man (1). The causative organisms are members of the family Mucoraceae, which belongs to the mucorales of the class Zygomycetes. They are saprophytes commonly found in soil and decomposed vegetation with a worldwide distribution. Depending on the immunologic status of the host, the disease may manifest in six different forms depending on the affected site: rhinocerebral, pulmonary, cutaneous, gastrointestinal, central nervous system, or miscellaneous (2). Rhinocerebral mucormycosis is the most common form and is subdivided into three subtypes: rhinomaxillary, rhino-orbital and rhino-orbito -cerebral, the latter form has a higher mortality rate(2). The primary mechanism of infection in this form is through inhalation of spores(3). Once the fungus gains entry into the body and begins to grow, hyphae invade tissues, especially blood vessels, causing thrombosis and tissue necrosis(2). Most cases of mucormycosis occur in immunologically or metabolically compromised hosts, and the rhinocerebral form is most often seen in diabetic patients, being particularly associated with ketoacidosis(4-6). During 1966-1996, only 14 well documented cases of fulminant rhinocerebral or paranasal mucormycosis were reported in otherwise healthy subjects(7). But most of them had local compromising factors such as polyps and chronic sinusitis. The keys to management are reversal of the underlying cause of compromised immunity, diabetic ketoacidosis or neutropenia, and appropriate antifungal therapy and surgical debridement of the affected tissue (8). Patients usually complain of
headache, rhinorrhea or epistaxis along with black nasal or oral masses (9). Progression can lead to orbital cellulitis, orbital apex syndrome, cavernous sinus thrombosis, and eventually fatal involvement of central nervous system. The diagnosis is made histologically because the disease is a tissue invasion and tissue reaction rather than the mere presence of such ubiquitous fungi that characterize the disease. Culture is used for the identification of specific species.6 In this article, we report a case of a fulminant rhino-orbito-cerebral mucormycosis in a healthy subject with no history of a known systemic disease.

Case Report:

A 51 year-old otherwise healthy man was referred to the emergency ward of Tehran/Taleghani Hospital with a 2-day history of headache, rhinorrhea and facial edema. A general practitioner suspected maxillary sinusitis and initiated therapy with Amoxicillin plus Augmentin. Physical examination revealed facial edema, patchy black discoloration of hard palate, rhinorrhea, excessive lacrimation from the left eye, periorbital swelling and ophthalmoplegia in the left eye; however, the eye fundus and vision were normal (Fig.1).

On admission, the patient had fever (38.9° C) and malaise and the disease seemed to aggravate over time. Laboratory tests revealed leukocytosis (15/8 x 10^9/L) with neutophilia and elevated C-reactive protein (185mg/L). There were no signs of hyperglycemia or ketoacidosis. Fasting blood sugar (106) and GTT (200) were within the normal range. Negative history of diabetes mellitus and other illnesses reported by the patient and his family members indicated that there was no reason to think of any previous medical condition compromising the patient’s general health status. Computed tomography (CT) scan was immediately obtained which showed partial opacification of maxillary, ethmoid and frontal sinuses and obvious extension of inflammatory process to the left inferomedial orbital wall, which caused anterolateral displacement of the eye globe (Fig. 2,3). No clear collection or bony erosion was found, and the brain seemed to be intact.

Figure 2- CT scan shows gross opacification of paranasal sinuses

Figure 3- CT scan shows left eye proptosis

A few hours later, facial swelling and pain became more intense. Ophthalmoplegia,
limitation of extraocular movement and chemosis appeared to progress especially in the left eye. Visual acuity in the left eye severely decreased and the patient only had light perception and was not able to count fingers. With the progression of the left eye involvement, the right eye swelling was aggravated and the fatal progression of the right eye involvement was noticed. Considering the extensive tissue destruction and the black, necrotic lesion on the palate, mucormycosis fungal infection was suspected and intravenous administration of amphotericin B, 1.5mg/kg/day and broad spectrum antibiotic was initiated for the patient. Culture for the fungal infection was also performed. Within 24 hours, with the clinical diagnosis of mucormycosis infection, urgent debridement of all infected tissues was performed through total maxillectomy, removal of nasal septum and ethmoidal content (Fig 4). The removed materials were sent for fungal culture and histopathological study (Fig 4).

**Discussion:**

Mucormycosis has found to be associated with numerous predisposing clinical conditions. Among the most recognizable risk factors for the development of rhino-cerebral mucormycosis (RCM), we may name the poorly controlled diabetes, hematologic malignancies, acquired immunodeficiency syndrome, severe burns, renal disease, malnutrition, and iatrogenic immunosuppression after organ transplantation. Only a few cases of mucormycosis have been reported in patients with no predisposing factor. Rhizopus is the predominant pathogen, accounting for 90% of the cases of rhinocerebral mucormycosis. It can be found in fruits, soil, dust, and manure and has been cultured from nasal mucosa of normal persons, where it may not cause clinical signs of infection. The organisms are aerobic but can live 2 to 5 days in vitro (11). Although infection usually occurs after inhalation through the nose, skin laceration can also be the port of entry. Mucorales hyphae have a predilection for growth in arteries and lymphatic system. These fungi also invade the nerves, adipose tissues, and bones; muscles are usually spared. Angioinvasion by the hyphae produces a fibrin reaction resulting in subsequent development of “mucor thrombi,” which occlude the arteries and lead to ischemia, infarction, and consequent formation of black necrotic tissue which is characteristic for RCM. Vascular occlusion prevents the systemic antifungal agent from reaching its target location, and ischemia favors the development of acidotic tissue, which is ideal for fungal growth (12,13). Since mucormycosis often invades blood vessels, infarction, necrosis, and
thrombosis are among its major characteristics (14,15). There are several pathways through which an infection can reach the cavernous sinus. The valveless superior and inferior ophthalmic veins allow 2 way communications between the face, nasal cavity, pterygoid plexus, and the dural sinuses, including cavernous sinus. Therefore, an infection from the maxillofacial region can potentially enter the cavernous sinus directly or by the reverse flow from various veins. Besides the hematogenous spread, rhinocerebral mucormycosis may disseminate through perineural invasion(16). Patients with rhinocerebral mucormycosis usually present with facial pain, headache, and fever. If the infection extends to the nasal turbinates and the orbits are involved, proptosis, periorbital edema, chemosis, ophthalmoplegia, and loss of vision may occur. If the disease invades the mouth, a black, necrotic scar is often found in the palate. When the clinical picture includes the presence of sinusitis with black discoloration in the nose and palate in addition to a predisposing factor, a diagnosis of RCM should be highly suspected. However, a tissue biopsy is necessary to confirm the diagnosis. The only definite way to diagnose mucormycosis is to visualize the characteristic hyphae in the tissue (17). Radiographic findings are helpful in assessing the different stages of the disease rather than in making a definitive diagnosis because the radiographic features may be indistinguishable from those of rhinosinusitis. In fact, during the early stages of RCM, normal imaging features may even be found. Bony erosions will appear late in the progression of disease. The standard medical therapy for RCM includes amphotericin B in a dose of 1.0 to 1.5 mg/kg/day for a period of several weeks to several months, depending on the clinical response and the degree of the drug’s side effects, especially nephrotoxicity. Prognosis of RCM primarily depends on two factors: early diagnosis and resolution of the predisposing condition. Survival is positively correlated with the time of diagnosis and initiation of treatment (18). In this case, no specific predisposing factors were detected accompanying the progression of RCM. The patient did not have any history of prior illness or hospitalization. He might have had some sort of occult condition such as mild type adult diabetes but the condition did not have any other manifestation. Local factors in the paranasal sinuses like polyps or chronic sinusitis might have helped the progression of disease. The reason for rapid progression and refractory form of rhinocerebral mucormycosis in this otherwise healthy patient remained unclear for us.

Conclusion:

In rare cases, rhino-orbito-cerebral mucormycosis can rapidly invade paranasal sinuses and result in patient's death.

References