Original Research Article

Clinical Experience of Rhino-orbito-cerebral Mucormycosis: Retrospective study of 18 cases

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Abstract

Background: Rhino-orbital-cerebral mucormycosis (ROCM), acute and aggressive fungal infection, usually occurs in several immunocompromised states. Patients manifest with signs and symptoms relating to the involved tissues. Treatment includes control of metabolic abnormality, administration of amphotericin B and surgery. In this retrospective study we evaluated the clinical features and outcome of treatment of 18 cases of rhino-orbital and ROCM in relation to the early diagnosis and intervention and predisposing co-morbid systemic conditions. **Material and Methods:** In this retrospective study, 18 consecutive patients with a diagnosis of ROCM and ROM were reviewed. All were treated with Amphotericin-B and nine with ROM underwent surgical debridement in addition. All were followed up to 11 months and outcome was analyzed. **Results:** Sinusitis, pharyngitis, or nasal discharge (84.21%) was the most frequent presentation followed by orbital or periorbital pain (73.68%). Nine patients with RO diagnosis and treated with surgical debridement along with Amphotericin-B survived and all the nine patients with ROCM died. **Conclusion:** Patients who received surgical treatment in addition to amphotericin B had a better outcome than those who received amphotericin B alone. Uncontrolled diabetes mellitus was the most common risk factors. A high index of suspicion and improved laboratory diagnosis are important for improving the outcome of this devastating fungal infection.

Keywords: Rhino-orbital-cerebral mucormycosis, diabetes mellitus, Amphotericin-B, surgical debridement, survival.

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INTRODUCTION

Mucormycosis is an acute, fulminant and fatal fungal infection in humans[1,2]. It is characterized by the presence of broad aseptate filamentous fungi branching at right angles with a predilection for intravascular invasion[3]. Rhino-orbital-cerebral mucormycosis (ROCM) is an uncommon, acute, and aggressive fungal infection occurring in several immunocompromised states including diabetes, which is the most common (60%–81%) predisposing factor[1,5]. The disease originates in the nasal/ sinus mucosae after inhalation of fungal spores and takes a rapidly progressive course extending to neighboring tissues, including the orbit, and sometimes to the brain. ROCM causes a very high residual morbidity and mortality due to the angioinvasive property of the fungus, thereby causing vascular occlusion and consequently resulting in extensive tissue necrosis[2]. Usually, it starts in the sino-nasal tissues (limited sino-nasal disease), progresses to the orbits (limited rhino-orbital disease) and finally affects the central nervous system (rhino-orbito-cerebral disease). Patients manifest with signs and symptoms relating to the involved tissues. The progression of the disease to the orbits produces pathgnomonic signs and symptoms, which helps in early diagnosis and treatment[5]. ROM cases are most commonly treated with aggressive surgical debridement of all involved tissues including exenteration of involved orbits along with prolonged administration of Amphotericin B[6,7]. Impaired delivery of the antifungal drugs to the site of infection because of vascular thrombosis and limited

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aggressive surgery because of the complex anatomy of the rhino-orbital region cautions for early diagnosis and aggressive management in these patients. As mucormycosis may involve the orbit and other ocular structures, the ophthalmologist may be the first physician to see a patient with this highly morbid condition. Thus, it is important to have this disease in the differential diagnosis, as a delay in diagnosis may be fatal. In this retrospective study we evaluated the clinical features and outcome of treatment of 18 cases of rhino-orbital (ROM) and rhino-orbito-cerbral mucormycosis (ROCM) in relation to the early diagnosis and intervention and predisposing co-morbid systemic conditions.

MATERIAL AND METHODS

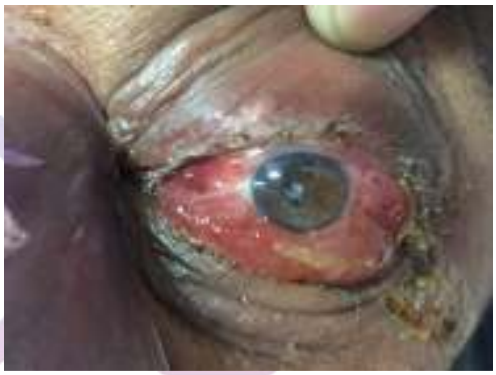
In this retrospective study, 18 consecutive patients with a diagnosis of ROCM and ROM were reviewed. Out of 18 patients, 12 were males and 06 were female. Their ages ranged from 45 to 72 years. Patients having smear and/or histopathological evidence of mucormycosis only were included. The study was approved by the institute's ethics committee. The diagnosis of mucormycosis was based on direct microscopy of aspirate/crusts from the nasal/sinus mucosae with culture on Saboraud's Dextrose agar and on histopathology. Three patients had type 1 diabetes, 15 had type 2 diabetes, and one had alcoholic liver disease (ALD). Nine patients had Chronic renal failure (CRF), two were HIV-1 positive. Nine had ROCM and the remaining nine had ROM involvement. Their clinical, biochemical, radiological (computed tomography/magnetic resonance imaging), and treatment profiles (amphotericin B and appropriate surgical intervention) were recorded and analyzed.

RESULTS

In this retrospective study, 18 consecutive patients with a diagnosis of ROCM and ROM were reviewed. Out of these 18 cases, nine were diagnosed as ROM and nine as ROCM. Clinical features of these patients are summarized in tables 1. Sinusitis, pharyngitis, or nasal discharge (84.21%) was the most frequent presentation followed by orbital or periorbital pain (73.68%). Abrupt visual loss (10.52%) was observed in 2 patients at presentation.

Table 1: Clinical features of study population (n=18)

Signs and Symptoms	Number of Patients	Percentage (%)
Sinusitis, pharyngitis, or nasal discharge	16	84.21
Orbital or periorbital pain	14	73.68
Cellulitis of face or lids	12	63.15
Proptosis	11	57.89
Black eschar of skin, nasal mucosa or palate	5	26.31
Numbness of homolateral side of face	4	21.05
Abrupt visual loss	2	10.52



Photograph 1: A male patient with initial presentation of ROCM

All the included patients were found to be immunocompromised. 18 patients were diabetic, 10 patients with uncontrolled diabetes and ketoacidosis. Whereas, CRF was present in 9 patients with final diagnosis as ROCM. Two patients with ROCM were found to be HIV-1 reactive in addition to diabetes and CRF.

Table 2: Summary of the ROCM patients (n=9)

SN	Age (yrs) / Sex	Comorbidity	Involvement	Intervention	Status
1	72 / M	DM, CRF	ROC	Amphotericin B	D
2	70 / M	DM, CRF	ROC	Amphotericin B	D
3	65 / F	DM, CRF	ROC	Amphotericin B	D
4	65 / M	DM, CRF	ROC	Amphotericin B	D
5	50 / M	DM, CRF, HIV	ROC	Amphotericin B	D
6	68 / F	DM, CRF, HIV	ROC	Amphotericin B	D
7	57 / F	DM, CRF	ROC	Amphotericin B	D
8	62 / F	DM, CRF	ROC	Amphotericin B	D
9	53 / M	DM, CRF	ROC	Amphotericin B	D

(DM= Diabetes mellitus; CRF= Chronic renal failure; D= Died)

Table 3: Summary of the ROM patients (n=9)

SN	Age (yrs) / Sex	Comorbidity	Involvement	Intervention	Status
1	49 / M	DM	ROM	Sx debridement + Amphotericin B	S
2	54 / M	DM	ROM	Sx debridement + Amphotericin B	S
3	62 / F	DM	ROM	Sx debridement + Amphotericin B	S
4	71 / M	DM	ROM	Sx debridement + Amphotericin B	S
5	70 / F	DM	ROM	Sx debridement + Amphotericin B	S
6	45 / M	DM	ROM	Sx debridement + Amphotericin B	S
7	59 / M	ALD	ROM	Sx debridement + Amphotericin B	S
8	55 / M	DM	ROM	Sx debridement + Amphotericin B	S
9	67 / M	DM	ROM	Sx debridement + Amphotericin B	S

(DM= Diabetes mellitus; ALD= Alcoholic liver disease; Sx debridement = Surgical debridement; S= Survived)

All the 18 patients were treated with Amphotericin-B with total doses varying from 3.0–3.5 g, and nine patients were subjected to appropriate surgery including lateral rhinotomy, sinusectomy, orbital exenteration and frontotemporal craniotomy. After surgery two patients had diminution in vision and the one had stroke. Nine patients with RO diagnosis and treated with surgical debridement along with Amphotericin-B survived and all the nine patients with ROCM died. Duration of follow up ranged from 6 months to 11 years.

DISCUSSION

Mucormycosis, also known as Zygomycosis was first described by Paultauf in 1885[8]. It is an acute opportunistic infection caused by broad, nonseptate saprophytic fungus found in soil, air, bread mould and rotten fruit and vegetables. The fungus belongs to the Zygomycetes class, the most common genera are *Mucor*, *Rhizopus*, *Absidia* and *Basidiobolus*. Mucorales species are vasotropic, causing tissue infarctions, and the mucormycosis spectrum ranges from cutaneous, rhinocerebral, and sinopulmonary to disseminated and frequently fatal infections, especially in immunocompromised hosts[9,10]. The infection develops after inhalation of fungal sporangiospores into the paranasal sinuses and infection spreads along vascular and neuronal structures and infiltrates the walls of blood vessels. Infection causes erosion of the bony walls of the ethmoid sinuses and the infection spread into the orbit and retro-orbital area and into the brain (rhino-orbital-cerebro-mucormycosis). Death may occur from cerebral abscess. Infection by this organism usually complicates any underlying chronic disease, such as diabetes mellitus, chronic renal failure or retroviral diseases. Despite advances in diagnosis and treatment, a high mortality rate of 30-70% still exists for this disease[11]. Death may occur within two weeks if untreated or unsuccessful treated.

In present study, sinusitis, pharyngitis, or nasal discharge (84.21%) was the most frequent presentation followed by orbital or periorbital pain (73.68%). Abrupt visual loss (10.52%) was observed in 2 patients at presentation. Periorbital swelling and pain were observed in 66% and 43% of patients respectively by Bhansali A *et al*[12]. Yohai *et al* observed 43% and 11% patients with Periorbital swelling and pain respectively[1]. Orbital and nasal findings are the most common presenting symptoms and signs in ROCM patients[13,14]. Orbital involvement may include loss of function of the second, third, fourth and sixth cranial nerves with proptosis, ptosis, diplopia, orbital pain, central retinal artery occlusion and loss of vision[13,14]. Retrobulbar extension of the process may lead to decreased vision or blindness due to optic nerve injury or retinal artery occlusion[13,14]. Progressive extension of necrosis into the brain can lead to cavernous sinus thrombosis, exophthalmus, complete ophthalmoplegia and papilledema. In our study, black eschar of skin, nasal mucosa and palate was seen in five patients. A black necrotic eschar is the hallmark of mucormycosis. However, the absence of this finding should not exclude the possibility of mucormycosis.

All the included patients in this study were found to be immunocompromised. 18 patients were diabetic, 10 patients with uncontrolled diabetes and ketoacidosis. Several predisposing conditions have been reported in the literature[11] with diabetic ketoacidosis as most common[15]. Authors have reported diabetes mellitus as a predisposing factor for mucormycosis in 36%–88% of cases[12,16]. Patients with uncontrolled hyperglycemia, particularly those with ketoacidosis, are the most susceptible. Diabetic patients are predisposed to the mucormycosis because of the decreased ability of their neutrophils to phagocytize and adhere to endothelial walls. Furthermore, the acidosis and hyperglycemia provides an excellent environment for fungus to grow. Patients with liver disease rarely develop mucormycosis[3]. The occurrence of mucormycosis in HIV/ AIDS patients is rare[17]. In our study, two patients were found to be HIV infected. In a large retrospective study of 1630 autopsies of patients who died of AIDS from 1984 to 2002, Antinori *et al*[18] observed only 2 patients with mucormycosis.

Amphotericin B is partially effective therefore surgical debridement becomes essential[19]. Antral wash,

lateral rhinotomy, pansinusectomy, orbital exenteration, and some- times intracranial surgery are performed depending upon the extent of the disease. Delay in diagnosis and treatment, hemiparesis, bilateral sinus involvement, and facial necrosis are the factors associated with poor survival in ROCM. Yohai *et al* reported survival of 63% of patients with a lag time from seven to 12 days and 44% in those with a lag time of 13 to 30 days[1]. In Bhansali A *et al* study, 85% patients survived who had lag time from three to nine days, but only 55% survived with a lag time of 10 to 45 days[12]. Patients with hemiplegia, facial/eye lid gangrene, and cerebral invasion by mucorales had a poor survival in our study. Similar findings were observed by Yohai *et al*[1].

In present study, nine patients who received surgical treatment in addition to amphotericin B had a better outcome (survived) than those who received amphotericin B alone (died). This is in agreement with observations made by others[6, 20].

In conclusion, mucormycosis is a rare but emerging fungal infection with a high mortality rate. Uncontrolled diabetes mellitus was the most common risk factors for mucormycosis. The pleiotropic clinical manifestations and elusive presentation of mucormycosis often delay diagnosis, with resultant poor outcomes. A high index of suspicion for mucormycosis based on appropriate risk stratification and improved laboratory diagnosis are important for improving the outcome of this devastating fungal infection.

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