RHINOCEREBRAL MUCORMYCOSIS

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ABSTRACT

Introduction: Mucormycosis is a rare life threatening disease occurring in immunocompromised patients and is caused by fungi of the order mucorales. We present a case study of 5 patients who presented with advanced stage rhino cerebral mucormycosis to maxillofacial department in RMI.

Materials & Methods: All patients were biopsied and diagnosis confirmed histopathologically. Patients were treated with parenteral amphotericin. Area with fungal load was debrided surgically under general anaesthesia.

Results: The common factor in all these patients was uncontrolled diabetes mellitus. Two out of five patients survived and made full recovery. The crucial factor in survival of these patients seems to be early detection and aggressive management.

Conclusion: Rhinocerebral mucormycosis must be suspected and treated aggressively in immunocompromised patients to improve the chances of survival.

Key Words: Mucormycosis; Immunocompromised; Diabetes Mellitus; Amphotericin B; Antifungal Agents.

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INTRODUCTION

Mucormycosis is an angioinvasive infection caused by the ubiquitous filamentous fungi of the order Mucorales.[1] Its risk factors include uncontrolled diabetes mellitus, immunocompromised patients, extreme malnutrition, patients with burns and intravenous drug users. Some patients may not have any identifiable risk factors.[2,3]

Given the ubiquitous nature of these fungi, most humans are regularly exposed to these organisms. They, however, rarely develop clinical mucormycosis due to low virulence of the organism. The main route of infection is via inhalation but inoculation can occur via ingestion and trauma. Cutaneous disease can also occur through non sterile tape and wooden splints.[4,5]

It is estimated that 500 cases of mucormycosis occur in United States per year.[6] A US cancer center analysis showed that at autopsy, 0.7% of patients had the disease and 20 patients per 100,000 admissions suffered from it.[7] In another study, Kontoyiannis et al estimated that one year cumulative incidence of mucormycosis in stem cell transplantations was approximately 4 per 1000 cases while in organ transplant cases it occurs in 0.6 per 1000 patients.[8]

Here we present a case series of five patients that presented to the Oral and Maxillofacial Surgery department of Rehman Medical Institute.

MATERIALS & METHODS

This is a retrospective analysis of the five clinical cases that presented to us at the Oral and Maxillofacial Surgery Department of Rehman Medical Institute over a period of two years. These cases were treated using internationally recognized guidelines. An outcome analysis was then performed that looked into the age, sex, clinical presentation, co-morbidities, modalities of presentation and clinical outcome.

RESULTS

Most of the patients presented late. All of them had uncontrolled type 1 Diabetes Mellitus. Two of the five patients recovered (40%). Three patients died in spite of Medical and/or Surgical intervention (60% mortality).

Case studies

Case 1

A 65 years old gentleman was referred by the medical team at RMI with facial and palatal

necrosis. He had uncontrolled diabetes and mental confusion. His CT scan revealed extensive necrosis of paranasal sinuses and cerebritis. Clinical diagnosis of Rhinocerebral Mucormycosis was made. Microbiology and medical teams were involved and the patient was started on broad spectrum antibiotics and antifungals. Prognosis was discussed with the family. Decision was made against any surgical debridement. Patient expired few weeks following his discharge.

Fig 1: Facial necrosis

Case 2

A 28 years old gentleman was presented to maxillofacial department with palatal necrosis and loss of vision in the right eye. He had uncontrolled diabetes mellitus and mental confusion. A biopsy was performed in Iran whose result was unavailable. Another biopsy was performed from the palate which showed Rhinocerebral Mucormycosis. The CT scan revealed extensive necrosis of maxilla, nasal and sinusoidal lining and brain abscess. Neurosurgery, ophthalmology, microbiology and medical teams were involved in the management. The patient was started on antifungals (Amphotericin B). A decision was made against any surgical intervention in view of poor prognosis. Patient was discharged on antifungals for 6 weeks. Patient was reviewed after 8 weeks in the clinic and a CT brain and face was performed which showed significant improvement in cerebritis. A surgical debridement of paranasal sinuses was performed. His right orbital contents were exenterated. The patient was discharged one week following surgery as he was making satisfactory recovery. Subsequently the patient made excellent recovery and after 3 months review was discharged.

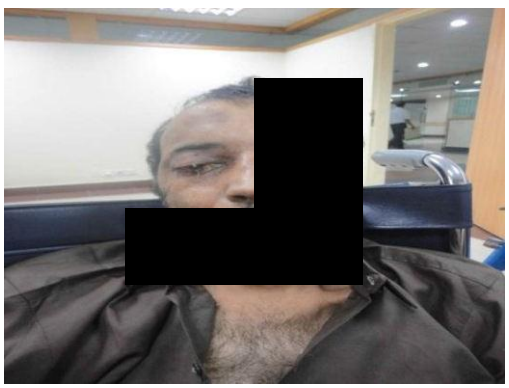

Fig 2a: Orbital cellulitis

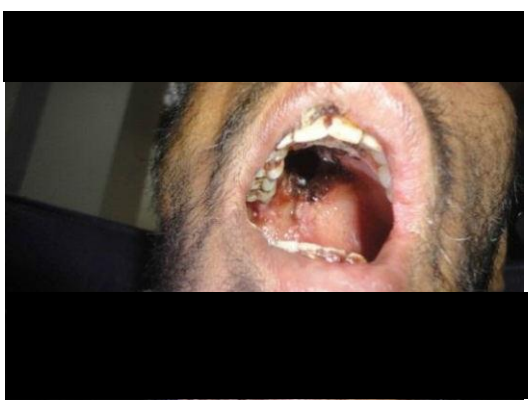

Fig 2b: Palatal necrosis

Case 3

A 60 years old woman with facial necrosis was referred to maxillofacial department from general surgery department. She had associated history of uncontrolled diabetes mellitus. A biopsy was performed from palatal region which showed Mucormycosis. CT scan of head, neck and brain revealed extensive necrosis of palate, maxilla, sinusoidal mucosa and right orbital contents with cerebritis. Microbiology,

ophthalmology, medical and neurosurgical teams were involved in management. Patient was started on antifungals (Amphotericin B). Prognosis was discussed with the family. Surgical debridement of nasal, maxillary, palatal and sinusoidal mucosa was undertaken. Right orbital contents were exenterated. Facial defect was reconstructed using bilobed flap. Patient however continued to deteriorate and expired 3 weeks following surgery.

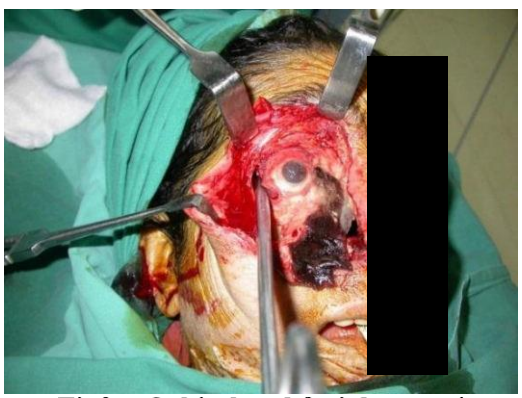

Fig3a: Orbital and facial necrosis

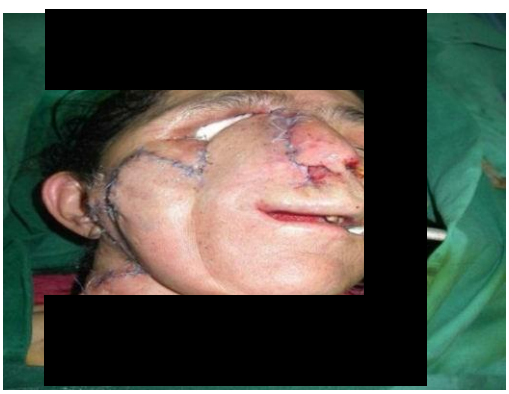

Fig3b: Reconstruction of defect

Case 4

A 40 years old patient presented with Rhinocerebral mucormycosis with associated history of uncontrolled diabetes mellitus. He was started on antifungals (Amphotericin B). Surgical debridement of paranasal sinuses and exenteration of left orbital contents was performed. Patient was discharged on parenteral Amphotericin B injections. Patient presented two months following discharge with complaint of dizziness, loss of appetite and pain in right side of face. Medical team was involved to control diabetes. He was continued on anti-fungal therapy and surgical debridement of right maxillary sinus was undertaken. Patient expired one week following the admission.

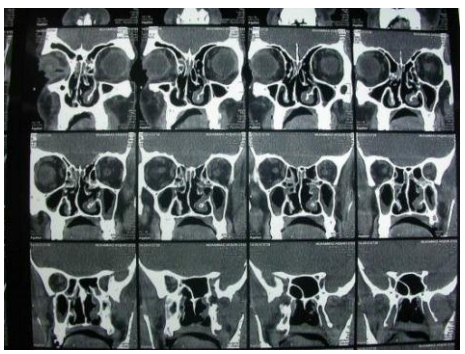

Fig4a: Sinusitis involving the paranasal sinuses

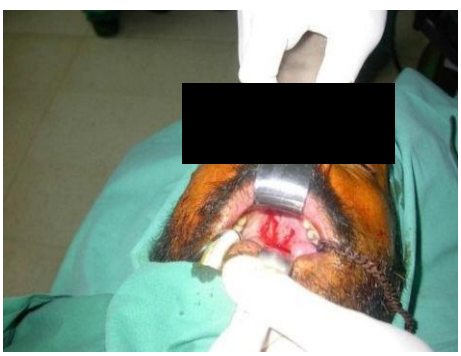

Fig4b: Palatal necrosis

Case 5

A 48 years old female with uncontrolled diabetes mellitus was presented to oral and maxillofacial department of Rehman Medical Institute with swelling and excruciating pain on left side of her face. On examination, no caries or periapical abscess was noted. Incision and drainage of left was performed. Histological examination revealed diagnosis of rhinocerebral mucormycosis. CT scan showed left nasomaxillary sinusoidal necrosis and infection. Patient was immediately admitted and was started on amphotericin B therapy. Surgical

debridement was then performed under general anesthesia. Patient made an excellent recovery.

Table 1 summarizes the major aspects of these five cases.

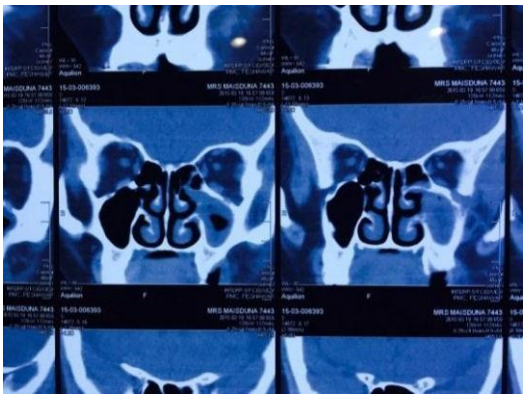

Fig5: Sinusitis involving paranasal sinuses

Table 1: Summary of the main aspects of five cases of Rhinocerebral Mucormycosis.

S #	Age (yrs)	Sex	Presentation	Co-morbidities	Treatment	Outcome
1.	65	M	Facial necrosis	DM type1	Antifungals	Mortality
2.	28	M	Palatal necrosis	DM type1	Antifungals Surgical debridement	Recovery
3.	60	F	Facial & palatal necrosis	DM type1	Antifungals Surgical debridement	Mortality
4.	40	M	Facial & palatal necrosis	DM type1	Antifungals Surgical debridement	Mortality
5.	48	F	Facial pain	DM type1	Antifungals Surgical debridement	Recovery

DISCUSSION

Mucormycosis mainly affects immunocompromised patients. In diabetic ketoacidotic patients due to low pH and hyperglycemia, neutrophils become dysfunctional and develop impairment in chemotactic ability. They also acquire decreased ability for intracellular killing by both oxidative and non-oxidative mechanisms.[9] Interestingly mucormycosis does not affect AIDS patients which indicates that T lymphocytes are probably not critical for fungal proliferation .[10] Artis et al demonstrated in 1982 that level of unbound serum Iron plays a critical role in predisposing diabetic patients to mucormycosis.[11] Rhizopus Oryzae infection are also characterized by angioinvasion which they cause through endothelial cell damage.[12] It results in vascular thrombosis and tissue necrosis.[13] In absence of viable blood supply to the infected area, it becomes difficult for leukocytes and antifungal agents to reach the foci of infection. Angioinvasion also contributes to the dissemination of disease.

Rhinocerebral mucormycosis usually presents with non-specific symptoms such as headache, nausea, and fever. Facial symptoms may include pain and numbness. There may be mucous or purulent discharge from the nose. Ocular symptoms range from peri-orbital pain to diplopia and blindness. The patient may suffer from convulsions and dizziness if the disease has progressed to involve brain.[14-17]

The main stay of treatment for Rhinocerebral mucormycosis is Amphotericin B antifungal therapy with surgical debridement.[18,19]

Amphotericin B is available in conventional (Amphotericin B Deoxycholate) and lipid complex formulations. These agents mainly act by inhibiting fungal cell membrane formation and by impairing its integrity. It may also alter the RNA and DNA metabolism and can lead to accumulation of peroxides that are toxic to the fungal cells.

The standard dose of Amphotericin B Deoxycholate is of 1-1.5mg/kg/d. Generally a treatment of 4-6 weeks is required; the optimal duration of treatment remains to be resolved.[20] Monitoring of the renal function in these patients is mandatory as it can cause nephrotoxicity. Doubling of serum Creatinine (>2.5 mg/dl) is an indication of change to lipid complex formulations, given in dose of 5mg/kg/d.[6] The dose may be increased to 7.5-10mg/kg/d, particularly when brain is involved.[21] The benefit of higher dose, however, is not proven and may cause nephrotoxicity.[22]

Liposomal Amphotericin B is a type of lipid preparation of Amphotericin B within lamellar liposomes. It was first reported by Fisher in 1991 to be effective against Rhinocerebral Mucormycosis .[23] Since then several papers have confirmed its efficacy and recommend it as first line of treatment due to its higher therapeutic potential and lower nephrotoxicity .[24,25] Survival rate of 67% is reported as compared to 39% with Amphotericin B Deoxycholate.[26]

Posaconazole is usually considered as the second line of treatment for Rhinocerebral Mucormycosis. It is a triazole and a typical dose is 400mg bd. Vehreschild et al[27] in a study of 96 patients showed that Posaconazole achieved a complete response in 64.6% patients, partial response in 7.3% patients and stabilized disease in 1%; the overall mortality was 24%. Posaconazole is also used as a sequential therapy following initial treatment with liposomal Amphotericin B.[28]

Roden et al[29] in a review of 929 cases stated that because of blood vessel thrombosis and tissue necrosis, the antifungals poorly penetrate the site of function. The necrotic tissues must therefore be aggressively removed for complete elimination of mucormycosis. Almannai et al[30] used hyperbaric oxygen in conjunction with Posaconazole for rhino-orbital mucormycosis. Its affectivity, however, is not proven.

Rhinocerebral mucormycosis carries a mortality rate of 30-70%.[31]

Conclusion: Early suspicion, correct diagnosis and aggressive treatment are essential to improve the chances of survival in immunocompromised patients.

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