A Rare Case Report of Successfully Managed Rhinocerebral mucormycosis

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ABSTRACT

Rhino cerebral Mucormycosis is a potentially lethal fungal infection caused by filamentous fungi from Mucoraceae family. Incidence is more in developed and developing countries with temperate climatic conditions. The infection can manifest in six different ways, which include Rhino cerebral, pulmonary, cutaneous, gastrointestinal, central nervous system or disseminated forms, of which the Rhino cerebral form is the commonest. It is an acute and often lethal infection, which is most commonly seen in uncontrolled diabetic and immune compromised patients. A 45 year old female patient referred from another hospital for further management. The patient presents to the emergency department with the complaints of severe headache, ophthalmoplegia and ptosis of left eye. Symptoms where of progressive in nature, on the second day patient complained of reduced sensitization over left forehead and acute onset and rapidly progressing vision loss in left eye. The patient was reported to have a 3 year history of type 2 diabetes mellitus, which was poorly managed. Histopathological examination of the region of infarcts presence of Mucorales confirmed. Surgical debridement of the affected area was performed. The patient was initially treated with Conventional Amphotericin B, the patient was not able to tolerate the medicine, and she was then converted to liposomal Amphotericin B. Uncontrolled diabetes mellitus along with poor hygiene contributed to the development of Rhino cerebral Mucormycosis in this patient. Previous diagnosis of focal meningitis also delays the diagnosis of Rhino cerebral Mucormycosis. Rhino cerebral Mucormycosis can be ideally managed with systemic antifungal therapy using Amphotericin B. Treatment with Liposomal Amphotericin B is found better in terms of patient tolerance, acceptance, and lower side effect profile. Management with Conventional Amphotericin B should be performed only in patients with good kidney function. Prinitiation of both surgical and medical therapies can result in better patient outcome.

Keywords: Mucorales, Diabetic Mellitus, Conventional Amphotericin B, Liposomal Amphotericin B, Medical therapy, surgical debridement.

INTRODUCTION

Mucormycosis is a potentially lethal fungal infection caused by fungi of order Mucorales 1. This condition is most commonly seen in patients with uncontrolled diabetes mellitus or immune suppression. The most common causative agents generally are Mucor, Rhizopus, Rhisomucor, Absidia, and Cunninghamella genera 2. Out of this the most common causative fungi are Rhizopus and Rhisomucor. This fungus is ubiquitous in the environment, such as decaying vegetation, organic matter, etc.... and is capable of causing infection only when a suitable host is available. The fungus usually enters into the host through small cuts and wounds and through airways. Even though it enters the human body, it is capable of causing infection only if there is a decline in immune function 3. The infection can manifest in six different ways, which include Rhino cerebral, pulmonary, cutaneous, gastrointestinal, central nervous system or disseminated forms. Among which the Rhino cerebral form is the most common form with 30 – 50 % of incidence. The initial diagnosis is difficult due to its typical presentation of symptoms. The reason for failure of early diagnosis is the lack of special clinical features or manifestations. The only confirmation diagnosis for Rhino cerebral Mucormycosis is a histopathological demonstration of the organism in the affected tissue 4. The term Rhino cerebral stands for the site of infection happened, when infection occurs in the nasal passages, sinuses and brain. It is considered lethal because the infection extends to the orbit and brain.

The incidence of Mucormycosis is commonly seen in places with temperate climatic conditions 5. Incidence among male was almost triple compared to females. Prognosis is poor with high rates of mortality and morbidities. There was a documented evidence of poor prognosis for patients with facial necrosis, nasal deformity and hemiplegia. Rhino cerebral Mucormycosis is a rapidly progressing disease if left untreated; it can result in carotid artery occlusion, cavernous sinus thrombosis, and CNS infarction secondary to fungal thrombosis, leading to hemiparesis, hemiplegia, coma, and finally death. Death will occur within a period of 2 weeks if left untreated 6. A rapid diagnosis followed by proper medical and surgical care can bring nearly 80% survival rate. Usual management includes control of underlying disease, correction of metabolic abnormalities.
Morbidity among diabetes patients are found to be are better compared to non-diabetics .

Table 1: Clinical features of Rhino cerebral Mucormycosis

<table>
<thead>
<tr>
<th>Distribution</th>
<th>Developing and developed countries with temperate climatic conditions .</th>
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<tbody>
<tr>
<td>Predisposing factors</td>
<td>Haematological malignancies, prolonged and severe neutropenia, poorly controlled diabetes mellitus with or without diabetic ketoacidosis, iron overload, major trauma, prolonged use of corticosteroids, illicit intravenous drug use, neonatal prematurity, and malnourishment .</td>
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<tr>
<td>Clinical presentation and Findings</td>
<td>Recurrent high grade fever, throbbing headache, bilateral bloody rhinorrhea, Nasal congestion, headache, earache, ophthalmoplegia, unilateral Periorbital facial pain, acute vision loss, cerebral infarction or hemorrhage, ptosis of the eye, and sagittal sinus thrombosis, black necrotic intranasal, palatal eschar (most common), Multiple cranial nerve palsies, periorbital edema .</td>
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<tr>
<td>Objective evidence</td>
<td>Biopsy analysis of the suspected areas of infections first recommended CT for detecting destruction of peridontal tissues and bone MRI for identifying the intradural and the intracranial extent of ROCM, cavernous sinus thrombosis, and thrombosis of cavernous portions of the internal carotid artery. CSF finding is commonly atypical .</td>
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<tr>
<td>Management</td>
<td>Liposomal amphotericin B (5–10 mg/kg /day) combination with extensive early surgical debridement .</td>
</tr>
<tr>
<td>Outcome</td>
<td>Fatality rate 50% - 80% .</td>
</tr>
<tr>
<td>Preventive strategy</td>
<td>Modify and control environment which reduces risk of exposure to air-born fungal spores .</td>
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Case presentation

A 45 year old female patient was referred to our hospital after histopathological diagnosis of Rhino cerebral Mucormycosis, for its further management. On her admission to the emergency department, she reported severe headache, ptosis of left eye and ophthalmoplegia. After her initial assessment the patient was referred to ENT, ophthalmology and department of medicine for expert opinion and its future management. The patient was on anti-diabetic treatment with insulin and was using dual monotherapy as anti-platelet (aspirin) and anti-hyperlipidemic (atorvastatin) agents respectively. She was diagnosed with T2DM 2 years before, which become uncontrolled and was converted to insulin from past 6 months. Her medical history of Coronary Artery Disease and Dyslipidaemia were unknown. She was also on anti-TB medication for TB meningitis, which was diagnosed 3 months before. On admission, her blood sugar level was too high for that she was initially put on insulin infusion followed by a sliding scale. She completed her 2 months intensive ATT phase (with isoniazid, rifampicin, Pyrazinamide, and Ethambutol), and was currently on maintenance phase with isoniazid and rifampicin.

Systemic examination revealed presence of left nasal wall crest. Peripheral nervous system examination revealed left side tenderness. Her ophthalmic examination revealed left eye ptosis. Biochemical parameters showed 15.2% of HBA1C, serum glucose of 184mg/dl and total cholesterol of 283mg/dl. MRI and CSF examination details were available from previous hospital, where MRI was suggestive of optic neuritis and CSF examination showing atypical components. Histopathological examination of necrotic tissues confirmed diagnosis of Rhino cerebral Mucormycosis.

She was put on ceftriaxone 1g IV, twice daily for prophylaxis. Plan of action against her condition were to initiate medical management with Amphotericin B and surgical intervention with debridement of the infected area. Before initiating medication management, patient was referred to pulmonologist, nephrologist and ophthalmologist to get clearance to initiate Amphotericin B. Due to poor socioeconomic status of the patient, despite of the risks from conventional Amphotericin B the team was decided to initiate the same. The patient was not able to tolerate the initial loading dose of CAMB. There was a hypotensive episode for which patient was shifted to ICU and was managed with adrenergic agents. Followed by which there was a rise in Sr. creatinine from 0.9 to 3.7, and urea from 37mg/dl to 50mg/dl. Conventional Amphotericin B was stopped and LAMB was arranged. It was administered at a dose of 1mg/kg in 500ml of dextrose infusion with hydrocortisone (100 mg IV) as pre medication. The patient was also given insulin glargine (long acting insulin) night dose to cover nocturnal hypoglycemia due to due dextrose. Surgical management was planned as debridement of infected area. Low molecular weight heparin was initiated for VTE prophylaxis with a dose of 0.4ml SC morning and night. Other medications include Paracetamol 650 mg oral tablets for managing fever, omeprazole 20 mg IV once daily as PPI, a vitamin supplement, ondansetron when needed for nausea and vomiting. The patient was responding well with the therapy, her renal parameters show a decreasing trend. The patient was put on soft diet during her stay in hospital. The patient was registered as clinically relevant case under department of medicine. The LAMB was arranged by local purchase from the pharmacy the cost was managed by the hospital.
DISCUSSION

Mucormycosis or zygomycosis or phycomycosis is an infrequently encountered fungal infection, which was first explained by Paululauf in 1885\textsuperscript{1-3}. Which belongs to phylum Zygomycota, a subclass of Zygomycota includes the human infective fungi of order Mucorales and Entomophthorales. Among the different forms present Rhizopus oryzae is the most commonly isolated and identified, followed by Rhizopus microspores, and Absidia corymbifera. These are ubiquitous in soil, air, skin, body orifices, manure, spoiled food and dust. Infection usually occurs or patient will be at risk of infection when there is a compromise in immune status\textsuperscript{4,10}.

The annual incidence was quantified only in certain countries due to its rare occurrence. It is reported from both developed and developing countries with temperate climatic conditions. The annual incidence of US was found to be 1.7 per million. Almost 42 reported incidents were recorded in India among them majority are localized infections. The male to female ratio is found to be 2.95:1, and no reports were found regarding the difference in complexity between both genders\textsuperscript{5,11}. The infection is predominately found to be associated with patients with chronic poorly managed diabetes mellitus and diabetic keto acidosis, hematological malignancies, immune compromised patients with organ transplantation, chronic medication with corticosteroids, recreational drug use were some of the most commonly encountered risk factors for Mucormycosis. There was no successfully managed case reports found dated before 1950\textsuperscript{3}. Later, after the discovery of Amphotericin B in 1953 the majority of the initially diagnosed Mucormycosis cases were better managed. There was an estimated 70% increase in the survival rate from 1970-1978. There were no significant difference between the survivors and fatalities when evaluated with respect to d’ evidence, gender, and age and literacy rate\textsuperscript{3,5}.

Table 2: Different formulations of Amphotericin B\textsuperscript{14-16}

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<tr>
<th>Sl no</th>
<th>Formulation</th>
<th>Dose</th>
<th>Advantages</th>
<th>Disadvantages</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>CAMB (Conventional Amphotericin B)</td>
<td>1mg/kg qd</td>
<td>Less cost, 5 decades of clinical experience.</td>
<td>Highly toxic, Poor CNS penetration</td>
</tr>
<tr>
<td>2</td>
<td>LAMB (Liposomal Amphotericin B)</td>
<td>5-10 mg/kg qd</td>
<td>Less toxic, more penetration, better outcome</td>
<td>Expensive</td>
</tr>
<tr>
<td>3</td>
<td>ABCL (Amphotericin B liposomal complex)</td>
<td>5-7.5mg/kg qd</td>
<td>Less nephrotoxic, combination with other agents</td>
<td>Expensive, less effective than LAMB for CNS</td>
</tr>
<tr>
<td>4</td>
<td>ABCD (Amphotericin B colloidal dispersion)</td>
<td>3-4mg/kg/day</td>
<td>Less nephrotoxic</td>
<td>Febrile reactions are more</td>
</tr>
</tbody>
</table>

CAMB is considered as the standard therapy for invasive fungal infections. It should be administered at a dose of 1mg/kg four times in a day for Rhino cerebral Mucormycosis. The standard dose and duration of therapy is not standardized. However 1mg/kg/qd up to a maximum dose of 2.5-3 g is considered as most commonly followed dosage regimen\textsuperscript{16}. In spite of its proven track record, its well-known side effects and toxicity will sometimes require discontinuation of therapy despite a life-threatening systemic fungal infection\textsuperscript{15,17}. Its efficiency is further limited due to variation in response rates usually from 10% to 80%. Close monitoring
of renal function along with serum electrolytes are necessary to check for toxicity. Out of the 3 different lipids based formulations available, LAMB is the most commonly used forms due to its highest safety profile. However, high cost, infusion related reactions and difficulties with studying these agents lead to licensure for salvage therapy and to restrict its use as standard therapy. Even though there is an initial higher cost for LAMB, pharmaco economic study shows cost effectiveness analysis favors liposomal Amphotericin B over CAMB. This patient reported signs of nephrotoxicity after loading dose of CAMB. It was also accompanied by a hypertensive episode managed with nor epinephrine. Hence need to be converted into LAMB despite of its cost and other side effect profiles. LAMB was initially started with 1mg/kg infusion and slowly raised to the required dose of 5mg/kg. New medicine was well tolerated by patients. After initial stabilization, surgical debridement was performed after prophylaxis with LMWH. After successful initiation of both medical and surgical intervention, patient was later transferred to a less intensive care room.

Other classes of medicines available for management of Mucormycosis are posaconazole and iron chelation therapy is recommended for refractory infected. Deferasirox is a newer iron chelater approved by FDA for use in Europe and India.

Reversal of underlying predisposing condition, and clinical state based surgical interventions are likely to improve the survival rate. Quality of life and economic burden of the disease is so far not quantified for Rhino cerebral Mucormycosis. There are no specific clinical endpoints exists apart from the absence of signs and symptoms. The possibility of reinfection is not well documented in literature. Hence the absence of radiographic or clinical evidence of infecting more than 2 years after treatment could be developed as a clinical end point.

CONCLUSION
Rhino cerebral Mucormycosis is a rare, complex and severe invasive fungal infection. The survival rate and morbidities from the infection is high. Appropriate management of the disease can be achieved by timely medical and surgical intervention. The quality of life and economic consideration must also be considered for better patient outcomes.

Outcomes
1. Patients with neurologic and ophthalmic symptoms along with uncontrolled diabetes or with poor immune function should be screened for Mucormycosis.
2. Surgical debridement of the necrotic tissue and medical management with systemic antifungal therapy is necessary to improve survival rate.
3. Selection of proper formulation of Amphotericin B should be done by considering economic, side effect profile and tolerance.
4. Liposomal Amphotericin B is accepted widely over its conventional counterpart due to increased patient tolerance, can be given at a much higher dose, significantly low side effect profile.

Abbreviations
ABCD: Amphotericin B Colloidal Dispersion
ABLC: Amphotericin B Liposomal Complex
ATT: Anti Tubercular Therapy
CAMB: Conventional Amphotericin B
CNS: Central Nervous System
CSF: Cerebrospinal Fluid
CT: Computed Tomography
ENT: Ear Nose Throat
FDA: Food and Drug Administration
IV: Intra Venous
LAMB: Liposomal Amphotericin B
LMWH: Low Molecular Weight Heparin
MRI: Magnetic Resonance Imaging
PPI: Proton Pump Inhibitor
T2DM: Type 2 Diabetes Mellitus
VTE: Vascular Thrombo Embolism

REFERENCES


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