



## RHINOCEREBRAL MUCORMYCOSIS- A RARE LIFE THREATENING INFECTION- CASE REPORT OF A DIABETIC PATIENT AT MZUZU CENTRAL HOSPITAL, MALAWI.

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### Abstract

**Background:** Rhinocerebral mucormycosis is a life threatening fungal infection usually acute and often fatal. It is more aggressive among diabetic or immunosuppressed patients. It is a rare condition which has never been reported in our setting. This case is reported in order to create high index of suspicion for prompt intervention in resource limited setting.

**Case presentation:** A case of a 45 years old female diabetic patient with nasal discharge, periorbital pain, facial oedema, ptosis and a black eschar involving the entire nose. A clinical diagnosis of rhinocerebral mucormycosis was made at Mzuzu Central Hospital in Malawi.

**Conclusion:** Because of rapid progression and high mortality, prompt recognition, timely initiation of antifungal therapy and aggressive surgical intervention are critical in reducing morbidity and mortality associated with the disease.

**Key words:** Mucormycosis, diabetes mellitus, amphotericin B, Surgical debridement.

### Introduction:

Rhinocerebral mucormycosis, a rare opportunistic infection belonging to a group of invasive fungal infections- mucormycoses caused by filamentous fungi of Mucoraceae family, more especially Mucor, Rhizopus and Absidia genera<sup>1</sup>. Rhizopus species are the most common causative organism responsible for more than 50-60% of the cases of mucormycosis and 90% of rhinocerebral mucormycosis<sup>2, 3</sup>.

Mucormycosis was first described in 1885 by Paultaut<sup>4</sup>. The fungi are found in the soil, decayed organic matter, bread mould, rotten fruits and

vegetables. There is lack of comprehensive data on incidence and prevalence of mucormycosis,

however epidemiology varies among general population with an annual incidence rate of 1.7 and 0.9 cases per million in United States of America and France respectively<sup>5, 6</sup>.

Mucormycosis is classified into six major clinical forms on basis of clinical presentation and particular site of involvement: (1) Rhinocerebral, (2) Pulmonary, (3) Cutaneous, (4) Gastrointestinal, (5) Disseminated and (6) uncommon rare forms such as endocarditis, osteomyelitis, peritonitis

and renal infections<sup>7-9</sup>. Rhinocerebral mucormycosis and pulmonary are the most common and devastating syndromes of mucormycosis.

Mucormycosis is aggressive in poorly controlled diabetic patients or among immunologically incompetent individuals such as those with neutropenia, transplant patients, acquired immunodeficiency syndrome, hemochromatosis, hematological malignancies, and chronic corticosteroid treatment<sup>4,10</sup>.

Limited data is available on the epidemiology of rhinocerebral mucormycosis however, about 70% of the cases occur among diabetic patients<sup>11</sup>. After thorough search, no published data is available on rhinocerebral mucormycosis in Malawi and across sub Saharan Africa with only limited case reports published in West Africa.

Rhinocerebral mucormycosis is caused by inhalation of fungus that has been released into air. Infection usually begins in the nasal turbinates then spread rapidly to paranasal sinuses. From paranasal sinuses it spreads to orbital area, palate, sphenoid and cavernous sinuses and brain within few days, and cerebral vascular invasion may lead to haematogenous dissemination of the infection with or without mycotic aneurysm development<sup>12,13</sup>.

Patient may present with fever, rhinorrhea, headache, ocular pain, facial edema, proptosis, internal or external ophthalmoplegia, visual loss, multiple cranial nerve palsies and black eschar which may be seen in the nasal mucosa or palate followed by tissue necrosis of nasal mucosa and palate<sup>14,15</sup>. However, the classical triad of paranasal sinusitis, ophthalmoplegia with blindness and unilateral proptosis with cellulitis are typical to most of the cases.

Diagnosis is clinical, however, histopathology examination of biopsy specimens helps to confirm the diagnosis<sup>16</sup>. Radiological investigations are of paramount importance in evaluating the progression of the disease<sup>17</sup>.

Management of Rhinocerebral mucormycosis is based on treating the underlying predisposing factor, prompt initiation of antifungal therapy and timely surgical intervention<sup>18</sup>.

#### **Case Presentation:**

A 45-year-old female newly diagnosed diabetes mellitus referred from Karonga District Hospital with a five days' history of facial oedema, necrotic nose and reduced level of consciousness. Two weeks prior to admission, she was treated for respiratory tract infection at a health centre with oral antibiotics (amoxicillin)

but she did not improve then subsequently she was referred to a district hospital. Upon arrival at a district hospital, the patient was diagnosed with diabetes mellitus and was admitted for glycaemic control and treated for sepsis with intravenous antibiotics (Ceftriaxone). Her glucose level was ranging from 238 to 480mg/dl. While in the ward she continued to have fever despite antibiotics and negative malaria screening, she then developed nasal discharge, periorbital pain, facial oedema, ptosis and a black eschar involving the entire nose and her condition was deteriorating. She was then referred to Mzuzu Central Hospital five days after the onset of these clinical features.

On arrival at Mzuzu Central Hospital, she was critically ill, lethargic with GCS 13/15, febrile (38.9°C), hypotensive (BP 82/62), tachycardiac (Pulse rate of 119). Further examination revealed generalised facial swelling with pustules, bilateral ptosis and proptosis, chemosis with purulent discharge and dark patches on the conjunctiva. Examination of the nose revealed extensive necrosis with complete collapse of nasal cartilage as seen in Figure 1 below. In the mouth, there was ulceration with necrotic hemorrhagic patches on the hard palate mucosa extending to soft palate. The rest of the examination was unremarkable and she had no features suggestive of vasculitis. Initial investigation; full blood count showed leucocytosis with WBC of 21,000/mm<sup>3</sup>, neutrophilic predominant (93.1%), hemoglobin of 9.7g/dl, Platelets of 234. She also had prerenal failure with a serum urea of 348.8mg/dl, creatinine of 0.19mg/dl and hypernatraemia (173.7mmol/L) but normal potassium of 4.83mmol/L. Liver function tests were unremarkable.



*Figure 1: Before surgical debridement*

She was promptly initiated on insulin sliding scale, intravenous fluids and antibiotics. With high suspicion of rhinocerebral mucormycosis, she was also started on empiric systemic antifungal (intravenous fluconazole 800mg/day) as amphotericin B was being sourced from another tertiary facility also bearing in mind of her renal impairment.

Patient was admitted in ICU, underwent extensive surgical debridement and tracheostomy was done as seen in Figure 2 below. While in ICU her blood sugar was controlled, hypernatremia was resolving, blood pressure and urine output improved, fevers came down, leucocytosis improved from 21,000/mm<sup>3</sup> to 13.4/mm<sup>3</sup>, however, her level of consciousness deteriorated and unfortunately she died on fifth day of admission in the hospital. CT scan was not done because it is not available at our facility.



Figure 2: After surgical debridement

Table 1: Timeline of relevant data

Event	Day 1 & 2	Day 3, 4, 5, 6 & 7	Day 8, 9, 10, 11, & 12	Day 13	Day 14	Day 15	Day 17
Home							
Health center							
District hospital							
Admitted at central hospital (referral)							
Consultant review							
Debridement							
Death							

**Discussion:**

As reported in our case, Diabetes mellitus is a risk factor for development of rhinocerebral mucormycosis mainly due to defective immune system hence inability to resist mucormycosis through reduction of WBC chemotaxis and dysfunction of Polymorph nuclear and mononuclear leukocytes as a result of hyperglycemia<sup>19</sup>. It has also been suggested that acidosis impairs iron binding to transferrin resulting into free iron that promotes growth of the Rhizopus oryzae but not in alkaline Ph<sup>20</sup>. Therefore, good glycaemic control is of utmost importance to prevent this.

As seen in our case, most patients with rhinocerebral mucormycosis presents with variable grade fever, sinusitis, orbital cellulitis, facial pain, black necrotic eschar of hard palate or nasal cavity, facial pain and unilateral facial swelling<sup>14,15</sup>. Then the infection spreads locally to involve the sphenoid sinus, orbits, cavernous sinus and brain leading to proptosis, visual loss, ophthalmoplegia, cerebral infarctions. Mucorales may also invade blood vessels and cause necrosis of vessel wall and mycotic thrombi. Progression of infection to central nervous system may lead to development of altered level of consciousness which might be the case with our patient<sup>17</sup>. However, hypernatraemia may also have contributed to reduced level of consciousness. Focal neurological deficits with cranial nerve palsies can also occur mainly due to involvement of vascular structures or cavernous sinus thrombosis.

This disease presents with diagnostic dilemma as initial presentation mimics facial/orbital cellulitis, sinusitis and cavernous thrombosis, bacterial infections such as staphylococcus aureus, streptococcal and gram-negative species.

Timely diagnosis of rhinocerebral mucormycosis is of importance for appropriate management of the patient<sup>10</sup>. Clinical features compatible with mucormycosis herald high index of suspicion for rhinocerebral mucormycosis with prompt initiation of treatment. As seen in our case the patient reported five days after the onset of classical clinical features which led to delay in initiating therapy however, definitive diagnosis is made by histological examination of the biopsy<sup>21</sup>. Fungal culture provides further confirmation but large numbers of false negative results have been reported compared to direct histopathological examination of surgical specimens<sup>22</sup>.

Radiological imaging such as CT scans are essential in evaluating the progression of the disease however may not always correlate with

clinical findings<sup>17, 23</sup>. In our case neither CT nor MRI scan was done due to unavailability of the services.

A full blood count of our case showed leucocytosis with neutrophilic predominance which is consistent with other case reports<sup>24-26</sup>.

Management of rhinocerebral mucormycosis is based on three main principles: reversal of predisposing conditions, prompt initiation of antifungal therapy and surgical intervention when appropriate<sup>10</sup>. As reported in our case, glucose control was achieved however, there was delay in initiation of antifungal therapy and surgical intervention.

It has been reported that members of azoles drug group have been used to treat mucormycosis with varying outcome, but amphotericin B deoxycholate (AMP) remains the only licensed antifungal agent for mucormycosis. Although lipid formulations of amphotericin B are safe and efficient, it has been proved that Liposomal Amphotericin B (LAMP) is superior to AMP<sup>27</sup>. Unfortunately, the cost of LAMP may be prohibitive in a resource limited setting. Amphotericin B was still being sourced however, it would have been used with caution due to renal impairment. It is important to be vigilant in monitoring the side effects of amphotericin B.

Rhinocerebral mucormycosis is associated with extensive vascular thrombosis hence there will be poor drug delivery to the site of infection. Therefore, medical management with amphotericin B alone is not effective. Aggressive surgical debridement should be undertaken as soon as the diagnosis of rhinocerebral mucormycosis is suspected which may involve removal of all necrotic tissue, palate, nasal cartilage and orbit which may be disfiguring requiring reconstructive surgery.

Duration and doses of antifungal therapy are not well established due to lack of comparative studies, therefore it is recommended that therapy should continue until there is clinical resolution of symptoms and signs as well as reversal of the predisposing factor. Much as there has been considerable improvement in overall prognosis over the past fifty years in patients with rhinocerebral mucormycosis, mortality rate is still high of about 40% but localised disease has been reported to have low mortality rate of about 10%<sup>18, 28,29,30</sup>.

The major limitation of this case presentation could be lack of external validity.

#### **Conclusion:**

In conclusion, Rhinocerebral mucormycosis is rare, hence largely unknown leading to delayed diagnosis. Clinicians must be conscious of typical manifestations and maintain a high index of suspicion of this fungal infection. Because of rapid progression and high mortality, prompt recognition, aggressive surgical intervention, antifungal therapy and glucose control are of paramount importance to reduce morbidity and mortality.

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##### **• Competing interests**

The authors declare that they have no competing interests.

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