

## Rhinocerebral Mucormycosis in a Diabetic Patient: A Case Report with Brief Review

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### ABSTRACT

Mucormycosis is considered one of the most rapidly progressing and fulminant forms of fungal infection which usually begins in the nose and paranasal sinuses following inhalation of fungal spores. It is caused by organisms of phylum Zygomycota, the subphylum Mucormycotina which include genera *Absidia*, *Mucor*, *Rhizomucor*, *Rhizopus* etc. The incidence of mucormycosis is approximately 1.7 cases per 1,000,000 inhabitants per year. Mucormycosis affecting the maxilla is not rare because of rich blood vessel supply to the maxillofacial areas. Most common form of this infection is seen in the rhinomaxillary region and in patients with compromised immunity such as diabetes. Hence, early diagnosis of this potentially fatal disease and prompt treatment is of prime importance in reducing the mortality rate.

### INTRODUCTION

Mucormycosis (earlier known as phycomycosis or zygomycosis) is a rare opportunistic fungal infection caused by fungi belonging to the order-Mucorales and family- Mucoraceae. It was first described by Paultauf in 1885.<sup>1</sup> It represents the third most common angioinvasive fungal infection after candidiasis and aspergillosis.<sup>2</sup> It is rarely seen in healthy individuals and usually affects the immune-compromised individuals.<sup>3</sup> Due to altered immunity in compromised host, mucormycosis occurs with rapid proliferation and invasion of fungal organisms in the deeper tissues.<sup>4</sup> The various predisposing factors for mucormycosis are uncontrolled diabetes (particularly in patients having ketoacidosis), malignancies such as lymphomas and leukemias, organ transplant, long-term corticosteroid and immunosuppressive therapy, acquired immune deficiency syndrome (AIDS), renal failure, cirrhosis, burns and protein-energy malnutrition.<sup>5</sup>

Pathophysiology involves inhalation of spores through the nose or mouth or even through a skin laceration. Individuals with compromised cellular and humoral defence mechanisms may generate inadequate response. The fungus may then spread to the paranasal sinuses and consequently to the orbit, meninges, and brain by direct extension.

However, some patients with mucormycosis have no identifiable risk factors.<sup>6</sup> Successful management of this fatal infection requires early identification of the disease and aggressive and

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prompt medical and surgical interventions to prevent the high morbidity and mortality associated with this disease process.<sup>7</sup> We report here with a case of mucormycosis of the maxilla in a diabetic patient.

### CASE REPORT

A 50-year-old female patient came to the emergency with chief complaints of pain and swelling over left side of the face since last 3 days and discharge from left side of the nasal cavity. The patient was apparently asymptomatic 3 days back when she subsequently developed pain in the upper left maxillary region. Her medical history revealed that she was an undiagnosed case of diabetes for several years with random blood sugar level of 550 mg/dl (normal 70–140 mg/dl) and hypertensive for 2 years, for which she was on medication.

On external examination, there was a diffuse swelling over the left upper half of the face which was extending mediolaterally from the lateral aspect of nose to the outer canthus of the left eye and superoinferiorly from the supraorbital orbital region to 2 cm above the corner of the mouth, respectively. The skin over the swelling was shiny with black necrotic area on the left nasal ala. On palpation, the swelling was soft in consistency, tender with no local rise of temperature [Figure 1]. Eye movements were normal, and pupils were reactive. There was edema and congestion noted

in both palpebral and bulbar conjunctiva suggestive of orbital complications. Paraesthesia over left side infraorbital region with circumorbital edema over the left eye was noted. The facial expressions were normal. Based on the history and clinical findings, a provisional diagnosis of acute fulminant invasive fungal rhinosinusitis with orbital complication was made clinically. Differentials include osteomyelitis, chronic granulomatous infection, and deep fungal infections.

A computed tomography (CT) scan revealed hyperdensity of the maxillary antrum with destruction of all the boundaries of left maxillary, ethmoidal and sphenoid sinuses was noted extension in the orbit and facial musculature was also seen.[Figure 2].

On biochemical investigation, an elevated fasting blood sugar level, decreased hemoglobin (7.8 g %) and HbA1c level of 14.3 was noticed. Nasal discharge was subjected to microscopic examination which revealed necrotic material interspersed with fungal hyphae. These fungal hyphae were broad aseptate, ribbon-like hyphae and showed right angle branching at irregular intervals. [Figure 3(a)&(b)] Based on radiological and microbiological findings, a final diagnosis of acute invasive left rhinosinusitis due to mucormycosis with orbital complication was made. Her vision was at major threat.

The patient was referred to physician for increased blood sugar levels and decreased hemoglobin. Patient was put on human

insulin which was given in sliding scale. Subsequently, endoscopic debridement was done and dead tissue from the lateral wall of the nose was removed followed by middle and inferior turbinectomy of left side of nose and left uncinectomy, middle meatal antrostomy, ethmoidectomy, sphenoidotomy were performed.

The excisional biopsy send to microbiology lab revealed similar microscopic findings as that of primary sample. [Figure 3(c)]. Culture was put on double SDA medium (Saborauds dextrose agar with and without antibiotics) which after 48hrs of incubation showed floccose, dense, white hairy colony which later turned gray giving a typical "salt and pepper" appearance as sporangia matures.[Figure 4]

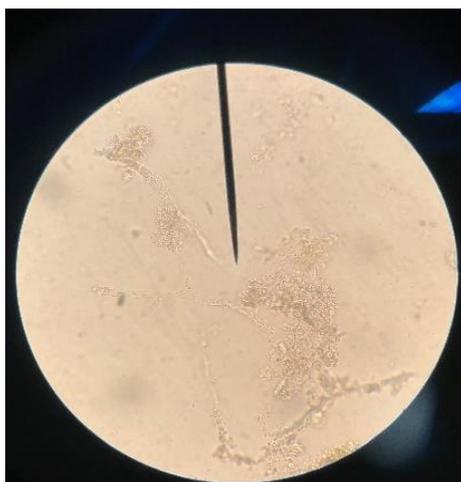
Further LPCB (lactophenol cotton blue stain) was done which showed blue coloured broad aseptate hyphae bearing sporangiophore which was long, seen till the next field which ends in a globose sporangium bearing oval and striated sporangiospores. Many collapsed sporangia with inverted umbrella appearance were also seen.[Figure 5(a),(b)&(c)]. On slide culture preparation findings similar to LPCB mount was seen. The patient was put on I.V amphotericin B which was later changed to liposomal preparation with strict KFT monitoring. After a month of treatment the patient condition improved and was soon discharged from the hospital with well healing nasal cavity and completely preserved left eye vision.



**Fig 1:** Rhinocerebral mucormycosis over the left maxillary region showing oedema and congestion. NOTE: necrotic area over left ala of nose.



**Fig 2:** Pre-op CT scan showing opacification of left maxillary sinus



**Fig 3(a):** Broad, hyaline, aseptate hyphae suggestive of zygomycetes.



**Fig 3(b):** Broad, hyaline, aseptate to pauciseptate hyphae, showing branching at right angle.



Fig 3(c): Aseptate hyphae showing kinking or collapsing at intervals suggestive of aseptate or pauciseptate hyphae.

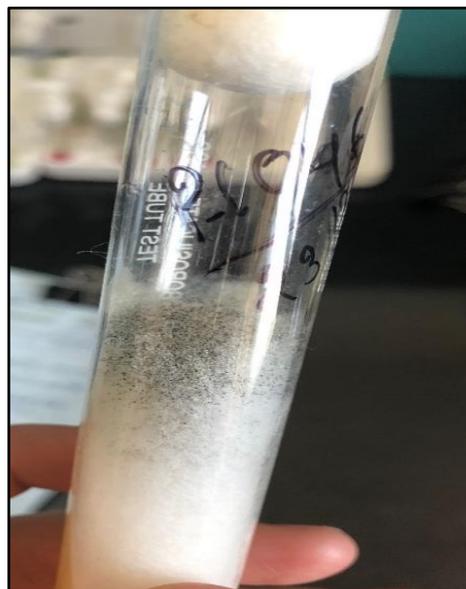


Fig 4: White cottony growth on the culture medium with typical "salt and pepper" appearance on its surface.

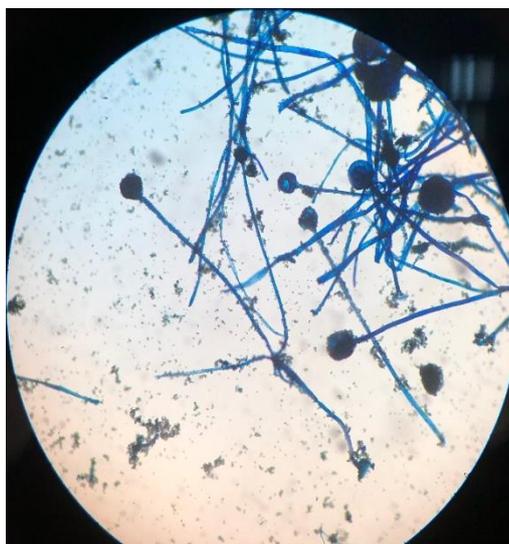


Fig 5a: (10x)- Nodal rhizoids adjacent to long and unbranched sporangiophore

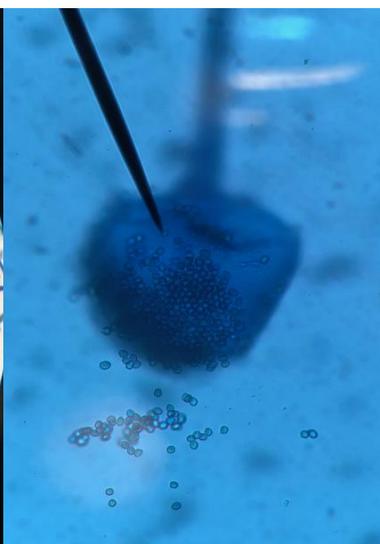


Fig 5(b): Large sporangia containing oval to round striated sporangiospores.

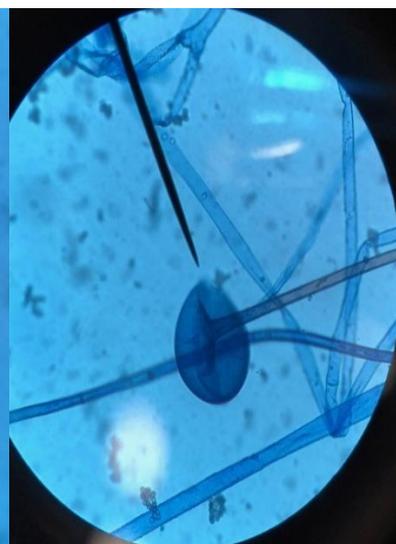


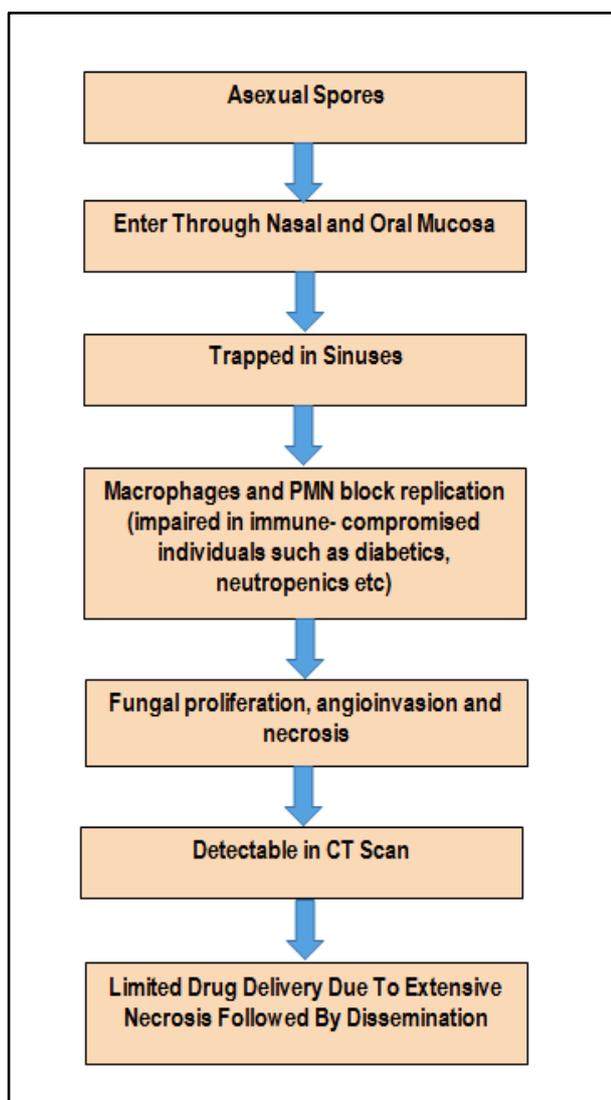
Fig 5(c): "Inverted umbrella" appearance of collapsed sporangia.

## DISCUSSION

Mucormycosis includes a range of infections caused by *Zygomycetes*, a class of fungi that produce broad, hyaline, branching ribbon-like hyphae and reproduce sexually by formation of zygospores. Pathogen can be found ubiquitously in soil, faeces and fruits and can also be cultured from the nasal passages, oral cavity and throat of healthy disease-free individuals. *Mucorales* is a subtype of *Zygomycetes*, which produces a distinct pattern of clinical infection. The fungi are usually avirulent; they become pathogenic only when the host resistance is exceptionally low. Ulceration in the mucosa can harbour entry for mucormycosis in the maxillofacial region, particularly when the host is immunocompromised.<sup>8</sup>

Infection by mucormycosis is caused by asexual spore formation. The tiny spores become airborne and settle on the oral and nasal mucosa of humans. In majority of immunologically competent hosts, these spores will be limited by a phagocytic response. In immune-compromised individual, this response fails and germination follows with development of hyphae. As

polymorphonuclear leukocytes are less effective in removing hyphae in such individuals and the infection becomes established. It further progresses as the hyphae begin to invade arteries, wherein they propagate within the vessel walls and lumens causing thrombosis, ischemia, and infarction with dry gangrene of the affected tissues. Hematogenous spread to other organs can occur (lung, brain, and so on) and results in sepsis.<sup>9</sup> [Chart 1]. Diabetes mellitus causes change in the normal immunological response of body to any infection, in several ways. Hyperglycemia stimulates fungal proliferation and also causes decrease in chemotaxis and phagocytic efficiency which permits the otherwise avirulent organisms to thrive in acid-rich environment. In the diabetic ketoacidosis patient, there is an increased risk of mucormycosis caused by *Rhizopus oryzae* as these organisms produce the enzyme ketoreductase, which allows them to utilize the patient's ketone bodies.<sup>8</sup> It has been established that diabetic ketoacidosis temporarily disrupts the ability of transferrin to bind iron, and this change eliminates a significant host defense mechanism and permits the growth of *Rhizopus oryzae*.<sup>10</sup>



**Chart 1: Pathophysiology**

In the present case, the patient presented with diabetes mellitus. The rhinocerebral (rhinomaxillary) form is the most common form of presentation commonly seen in patients with uncontrolled diabetes mellitus.<sup>11</sup> Others include rhinocerebral, pulmonary, and cutaneous forms (superficial) and less frequently, gastrointestinal, disseminated, and miscellaneous forms.<sup>12</sup> Patients with rhinomaxillary mucormycosis clinically present with facial pain, swelling and low-grade fever. The disease usually initiates in the nasal mucosa or palate extending to the paranasal sinuses and then spread through the surrounding vessels such as angular, lacrimal, and ethmoidal vessels. In addition, mucormycosis can also involve the retro-orbital region by direct extension.<sup>13</sup> Once fungal hyphae enter into the bloodstream, they can spread to other organs such as cerebrum or lungs which can be fatal for the patient.<sup>4</sup>

Clinical differential diagnosis of lesion should include chronic granulomatous infection such as tuberculosis, tertiary syphilis, squamous cell carcinoma, midline lethal granuloma, and other deep fungal infections.<sup>14</sup>

On radiography, opacification of sinuses may be noticed in conjunction with patchy effacement of bony walls of sinuses.<sup>5</sup> CT with contrast or magnetic resonance image scan can demonstrate erosion or destruction of bone and helps to know the extent of disease.<sup>14</sup>

Histopathologically, the lesion demonstrates broad aseptate fungal hyphae that show branching at right angles.<sup>5</sup> In the present case, the same histopathology was revealed. The histopathological differential diagnosis includes aspergillosis where the hyphae of *Aspergillus* species are septate, smaller in width and branch at more acute angles.

When diagnosed early, mucormycosis may be cured by a combination of surgical debridement of the infected area and systemic administration of amphotericin B for 3 months. Proper management of the underlying condition is also an essential aspect affecting the outcome of the treatment.<sup>15</sup>

## CONCLUSION

Mucormycosis is an aggressive fulminant invasive fungal infection that can occur in patients with diverse predisposing factors such as uncontrolled diabetes, renal failure, organ transplant, long-term corticosteroid and immunosuppressive therapy, cirrhosis, burns, and AIDS malignancies such as lymphomas and leukemias. In a diabetic patient, it can be triggered even by minor dental procedures such as tooth extraction. Further attempts should be made for the early diagnosis of this disease and prompt management of the patient.

## DECLARATION OF PATIENT CONSENT

The authors certify that they have obtained all appropriate patient consent forms. In the form the patient has given her consent for her image and other clinical information to be reported in the journal. The patients understand that their names and initials will not be published and due efforts will be made to conceal her identity, but anonymity cannot be guaranteed.

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