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# The Deadly Disease by Black Fungus – Mucormycosis, A Review

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**ABSTRACT**

Mucormycosis, earlier known as zygomycosis, is a severe angioinvasive highly fatal fungal infection caused by a saprophytic fungus, belonging to the class Mucormycetes. It presents itself in various clinical forms, rhino-orbit-cerebral being the commonest form. The immunocompromised status of the patient remains the main risk factor for the disease. Early diagnosis and timely medical and surgical intervention are imperative for the effective management of the disease.

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## INTRODUCTION TO MUCORMYCOSIS

India in 2020 saw an epidemic of a deadly disease commonly referred to as "Black Fungus" during the ongoing 2nd wave of the COVID-19 pandemic. The name was a misnomer as the fungus causing the disease was not black but the lesions it produced were blackish due to its ability to invade blood vessels and cause ischemia with subsequent tissue necrosis. (1)Mucormycosis, earlier known as zygomycosis, is a severe angioinvasive, highly fatal infection caused by common saprophytic filamentous fungi, belonging to class Mucormycetes. (2) In 1885, Platauf reported the first documented case of mucormycosis caused by *Rhizopus* species which was a systemic infection involving the rhinocerebral and gastric system. (3)It was in the early 1960s that culture identification became a routine part of the diagnostic procedure. A large proportion of 'mucormycosis' cases caused by Mucormycetes fungi, were originally classified under the genus *Mucor*. Later, these fungal species were reclassified into various families and genera within the order Mucorales. (4)

### Clinical presentations of Mucormycosis

A) The rhino-orbit-cerebral form is the most common clinical presentation of mucormycosis. Almost 2/3rd of these cases occur in diabetic ketoacidosis patients. Patients usually present with sinusitis-like symptoms such as sinus pain, drainage, and swelling which rapidly progresses to involve tissues of the periorbital region leading to proptosis and chemosis. Vessels become thrombosed leading to necrosis of involved tissue turning it black. The sinus infection may extend to the hard palate causing ulcerations. Optic nerve involvement causes loss of vision. Cranial nerve palsies may be observed in some. CNS invasion may follow leading to cavernous sinus thrombosis and internal carotid artery thrombosis. (5)However, the mortality has come down over the period from almost persistently fatal to 40%. (6)

B) Pulmonary mucormycosis is known to arise due to inhalation of fungal spores. This form is most commonly seen in patients of leukemia and lymphoma receiving chemotherapy. Patients present with fever, dyspnea, cough, and chest pain which is clinically indistinguishable from bacterial pneumonia and aspergillosis. Tissue necrosis due to angioinvasion results in cavitation and hemoptysis. A High-resolution CT scan is more of an aid than sputum and BAL cultures. Histopathology of biopsy specimen establishes the diagnosis. Hematogenous dissemination to other organs, if pulmonary mucormycosis is left untreated, leads to the disseminated form. This can increase the mortality from 50 to 70% in pulmonary mucormycosis to >95% in disseminated form. (6)

C) Cutaneous mucormycosis develops as a necrotic eschar which may arise following trauma, burns, or sometimes with no predisposing condition. Iatrogenic causes include infection at the injection site, catheter insertion site, and use of contaminated surgical dressings. Isolated cutaneous mucormycosis if treated promptly with surgical debridement has a good prognosis but, as the fungus is angioinvasive it soon invades the adjacent fat, muscle, and fascia causing necrotizing fasciitis and this has a mortality of 80%. (6) Sometimes aerial mycelium is produced at the site of the lesion which looks like white cotton, visible to the naked eye. (5)

D) Gastrointestinal mucormycosis arises from the ingestion of fungal spores. The patient is usually malnourished and presents with nonspecific abdominal pain, distension, nausea and vomiting, fever, and, hematochezia saw occasionally. It is commonly diagnosed post-mortem as the infection is acute and rapidly fatal, involving the stomach, colon, and ileum. A biopsy of the suspected area during surgery or endoscopy can help in establishing the diagnosis. Premature neonates may present with necrotizing enterocolitis. (6)(7)

E) The disseminated form may arise from any of the primary sites, with the pulmonary type having the highest incidence of dissemination. The brain is the most common site of dissemination associated with almost 100% mortality. (6)

A few cases of other uncommon sites such as bones, mediastinum, trachea, kidneys, and peritoneum have also been reported in the literature. (6) Onychomycosis and infections of the external ear are also reported. (5)(8) Isolated cerebral mucormycosis has also been seen in intravenous drug abusers which has a mortality of 60%. (9)

**Risk Factors Associated and Pathogenesis of Mucormycosis**

Mucormycosis can be a fatal infection occurring commonly in patients who are immunocompromised. (6)

***Mucormycosis and Diabetes mellitus***

Diabetic ketoacidosis (DKA) is most commonly associated with the development of mucormycosis primarily because of the failure of suppressing the spore germination and killing of proliferating fungal hyphae. (10)Ketoacidotic state (hyperglycemia and acidosis) induces a state of functional neutropenia by suppressing the chemotaxis, phagocytic activity,

and oxidative burst. (11) Also the free iron in serum of DKA patients is high which also supports the growth of Rhizopus spp. (12)

***Mucormycosis and Cancer***

Mucormycosis is usually seen in hematological malignancies (HM) such as leukemia and lymphoma. Pulmonary mucormycosis is the most common presentation and is diagnosed many times on autopsies. Chemotherapy given to these patients leads to neutropenia thus increasing the risk. Neutropenia with an absolute neutrophil count of less than 1000/ml for 1 week or more, is the major risk factor for patients undergoing chemotherapy. (13)(14)

***Increased susceptibility in transplant recipients***

Mucormycosis is a threat to stem cell transplant and solid organ transplant patients. The use of steroids and immunosuppressants is the main culprit in these patients. (15)

***Role of Iron uptake in the pathogenesis***

High levels of free serum iron increase the susceptibility to mucormycosis. Iron chelator, deferoxamine predisposes to Rhizopus infection by acting as a xenosiderophore delivering iron to iron uptaking molecules of the fungi, thus increasing the risk of mucormycosis in dialysis patients who are often treated with deferoxamine. (12)

***Intravenous drug use***

The association between mucormycosis and intravenous drug use has also been observed. (16) The spores are believed to be present in the illicit drug as the infection is seen far away from the injection point, like brain or heart valves. (5)

***Dental Extraction is a Risk Factor***

Many cases of mucormycosis, both oral and rhino cerebral forms have been reported following tooth extraction. A study in 2018 reported sixteen cases from the world over with nine cases from India. Dental professionals must be aware of the possibility of this serious complication, especially so in diabetic patients. (17)

***HIV and Mucormycosis***

HIV has not been associated as a significant risk factor in patients with mucormycosis. A review of 67 mucormycosis cases in HIV-infected patients revealed that HIV alone as a

predisposing factor was present only in 4 cases. Thus, it can be concluded that T lymphocytes necessarily are not critical for inhibiting fungal spore proliferation. (18)

***Nosocomial Mucormycosis***

In recent years, mucormycosis is increasingly being recognized as a nosocomial infection. A study revealed that 15.4% of mucormycosis cases were acquired from either intramuscular injections or incision & drainage procedures. (19)Another study revealed that 9% of cases acquired the infection through ECG leads, adhesive tapes, contaminated intramuscular injections, or air in the health care facility. (2) It was also observed that bandages, medication patches, intravenous catheters, wooden tongue depressors or antifungal prophylaxis could be associated with mucormycosis infection. (19)

***COVID Associated Mucormycosis* (CAM)**

COVID-19 in 2020 during the 2$^{nd}$ wave in India brought mucormycosis in limelight. The country was already dealing with the harsh 2$^{nd}$ wave of COVID-19 when this deadly disease gripped the country. Patients presented with features of mucormycosis usually after 3rd week of onset of COVID–19, however, the time of presentation was variable. The most common presentation was rhino-orbital-cerebral mucormycosis (ROCM) which presented as swelling on one side of the face, fever, headache, nasal or sinus congestion, and black lesions on the nasal bridge or upper inside of the mouth. COVID-19 infection may induce significant and persistent lymphopenia and deranged neutrophil-lymphocyte ratio (NLR) which predisposes the patient to increased risk. Various risk factors that could be attributed to, for development of CAM included hyperglycemia, neutropenia, overuse of steroids or broad-spectrum antibiotics, prolonged ICU stay, pre-existing co-morbidities, voriconazole prophylaxis, and use of deferoxamine. The Government of India made mucormycosis a notifiable disease under the Epidemic Diseases Act 1897. (1)

***Pediatric Mucormycosis***

A study conducted on pediatric mucormycosis revealed some interesting facts. The most common pediatric type was cutaneous (27%) followed by gastrointestinal (21%), rhinocerebral (18%), and pulmonary (16%). The most common species involved were *Rhizopus* species (44%) and then *Mucor* species (15%). Underlying factors included neutropenia (18%), prematurity (17%), diabetes mellitus (15%), and ketoacidosis (10%). The antifungal agent used was amphotericin B alone(73%) followed by a combination of

amphotericin B and another antifungal agent. 59% of patients had to undergo some surgery. Mortality was 36% in those who received therapy as compared to 88% in those who did not receive any therapy. Mortality rates were very high in cerebral, gastrointestinal, and disseminated types. (20)

**The environmental niche of Mucormycetes**

Mucormycetes are found to be ubiquitous. The spores of these fungi have been isolated from soil, grains, seeds, beans, nuts, and air and dust samples. *Lichtheimia corymbifera* was isolated from the corpse who lived approximately 5300 years ago. *Rhizopus* has been isolated from soil, grasslands, food items, etc. *Lichtheimia* species have been isolated from various moist and humid conditions like those in waterlogged grasslands. *Rhizomucor pusillus* has been isolated in various foodstuffs like grains, nuts, etc.(5)

**Growth characteristics of Mucormycetes**

Mucormycetes grow well on ordinary fungal media such as SDA without cycloheximide, potato dextrose agar, and oatmeal agar. They are usually rapid growers and colonies start appearing within 2-5 days. They usually have an erect mycelium which is fibrous, fluffy or cotton candy-like with little or no pigmentation on the reverse. On mature growth, some isolates reach the lid of the Petri dish and are known as lid-lifters. Once sporulation starts, a color begins to appear which may be white to tan, brown, grey, or even black. Most members sporulate on ordinary media except for *Apophysomyces* and *Saksenaea* species which may produce only sterile hyphae. Sporulation in such fungi can be stimulated by the water culture technique. (5)

**Microscopic features of Mucormycetes**

All species of Mucorales are characterized by the presence of a vegetative mycelium which is composed of wide ribbon-like aseptate hyaline hyphae that extends between two rhizoids. The mycelium bears an erect wide aerial hyphal element called sporangiophore which ends in sporangia. Based on the morphology of the predominant asexual spore-producing structure, Mucorales have been divided into three groups: sporangium producers, sporangia producers, and microsporangium producers. Most species are sporangium producers' including *Rhizopus*, *Rhizomucor*, *Mucor*, *Lichtheimia (Absidia)*, *Apophysomyces*, and *Saksenaea*. Two Mucorales, *Cunninghamella bertholletiae* and *Cokeromyces recurvatus*, produce

sporangioles. Merosporangium producer known to cause disease in humans is only one, *Syncephalastrum racemosum*. (5)

The most commonly isolated mucormycetes belong to the genus *Rhizopus*, *Lichtheimia*, and *Mucor* and *Rhizomucor* spp. *Rhizopus arrhizus* (*oryzae*) has been identified as the causative agent in 70% of cases. *Rhizopus microsporus* accounts for 15% of all cases. Rarely, *Saksenaea*, *Cunninghamella*, and *Apophysomyces* are isolated. (2)(5)

**Laboratory Diagnosis of Mucormycosis**

Diagnosis of Mucormycosis is based on collective assessment of presenting symptoms, microscopy, culture, imaging studies, and histopathology.

**A. Direct Microscopic Examination**

KOH wet mount is the first investigation to be performed on a clinical specimen for fungal hyphae visualization. Calcoflour white stain (CFW) preparation is a more sensitive alternative. Positive direct microscopy in the background of a clinical picture of mucormycosis, is suggestive of infection even in the absence of a positive culture report. Hemotoxylin & Eosin stain can also be performed from the necrotic background, however, it should be confirmed with a fungal-specific stain such as Periodic Acid Schiff (PAS) and Gomori's Methenamine Silver (GMS). These histopathological methods are more helpful in establishing a definitive diagnosis but take more time than a simple KOH preparation. Considering the aggressive nature of this infection, an early diagnosis is imperative. (5)

**B. Fungal culture**

Culture helps in fungal identification and studying epidemiology. Earlier, the culture positivity rate for mucormycosis was very low, approximately 20%, primarily due to the fragile nature of the hyphae. Also, the aggressive processing of the sample rendered the hyphae nonviable. (21) However with recent culture techniques involving minimal manipulation of the specimen, the positivity rate has increased to almost 71%. (7)

**C. Imaging Studies**

**A**mongst the imaging modalities, CT helps in defining the extent of invasion, especially in ROCM cases. It depicts the edematous mucosa and destruction of periorbital tissues and bone margins, however, bone involvement is often seen late in the course of infection. MRI helps

in identifying the intradural and intracranial extent of ROCM, cavernous sinus thrombosis, and thrombosis of cavernous portions of the internal carotid artery and perineural spread of the infection. (22)In pulmonary mucormycosis, wedge-shaped infarcts may be seen on chest imaging. (5)Reverse halo sign is more commonly seen in mucormycosis than in other pulmonary fungal infections. (23)

**D. Molecular Methods**

Molecular techniques have a limited role in primary diagnosis. They are being extensively used for determining taxonomic assignments. Molecular methods include sequence-based and non-sequence-based methods. Amongst the sequence-based methods, the targets include the ITS region, D1/D2 domain of the 28 S rRNA gene, and V9 region of the 18S rRNA gene. Non-sequence-based methods include PCR with RFLP, multiplex PCR, and Real Time PCR.(5)

Matrix-assisted laser desorption/ ionization time-of-flight (MALDI-TOF) can be used for better identification of species of Mucormycetes. Newer detection techniques like gene expression profiling, next-generation sequencing, and breath-based metabolomics are also being investigated. (1)

**Therapy for Mucormycosis**

Early diagnosis and treatment become very imperative in the management of mucormycosis as the disease tends to progress rapidly. There are four essential elements of therapy for mucormycosis: a. early diagnosis, b. correcting predisposing conditions like diabetic ketoacidosis, deferoxamine, immunosuppressive therapy, steroids, etc. appropriate antifungal therapy, and d. surgical debridement whenever required. (6)(24)

**A. Role of Surgical Debridement**

Timely surgical debridement is very important in the cases of mucormycos is to removing the infected and necrotic tissue and minimizing the further spread of infection. It has been shown to reduce mortality significantly in these patients. (6) In a case series of rhinocerebral mucormycosis, mortality was 70% in cases treated with antifungal agents alone versus 14% in cases treated with antifungal agents plus surgery. (25)Mortality was <10% when localized cutaneous mucormycosis was treated with aggressive surgical debridement and adjunctive antifungal therapy. (26) In pulmonary mucormycosis, 68% mortality was seen in patients

treated with antifungal agents alone, versus 11% in patients treated with antifungal agents plus surgery. (27)

**B. Medical Treatment for Mucormycosis**

***Amphotericin B***

Amphotericin B continues to be the mainstay of therapy for mucormycosis. (27) The lipid formulations being less nephrotoxic than amphotericin B deoxycholate can be safely administered at a dose of 5mg/kg/day for a prolonged period. (6)(27)Treatment with LAmB is associated with a survival rate of almost 67% as compared to the survival rate of 39% with amphotericin B deoxycholate. (6)This is usually said as a blanket statement for all Mucormycetes, however, the in vitro susceptibility results show that some species such as *Mucor* and *Lichtheimia* have lower MICs to AmB while *Cunnighamella* and *Rhizopus de*monstrate higher MICs emphasizing the need to perform antifungal susceptibility. (28)

***Posaconazole***

Posaconazole was the first drug of the azole family that demonstrated a broad spectrum of activity against mucormycetes, with an $MIC_{50}$ ≤1mg/L. It is considered the most effective salvage therapy for refractory mucormycosis or where the patient is intolerant to polyenes. (29)*Lichtheimia* species are considered the most sensitive species to posaconazole, *Saksenaea vasiformis* and *Rhizomucor* species have also exhibited low MICs for posaconazole whereas *Rhizopus* species and *Cokeromyces recurvatus* have shown a higher MICs.(29)Other clinical studies have also recommended posaconazole as salvage therapy for mucormycosis with no toxicity. (30)(28)

***Isavuconazole***

Isavuconazole is a second-generation triazole with a broad spectrum of activity against yeasts, molds, and dimorphic fungi. It was approved for the treatment of mucormycosis in adults by US Food and Drug Administration in March 2015 and the European Medicines Agency in July 2015. It seems to be a viable option in patients who are not able to tolerate amphotericin B or posaconazole therapy. (31)This was successfully demonstrated first by Ervens et al in a 45-year-old patient with *Rhizopus arrhizus* ROCM who was administered isavuconazole as a salvage agent as he was refractory to posaconazole and amphotericin B and the patient survived. (32)

***Itraconazole***

Itraconazole is considered to be active against a few Mucormycetes, in vitro. Mucormycetes exhibit a wide range of MICs for itraconazole (0.03-2mg/L). *Rhizomucor*, *Syncephalastrum*, and *Lichtheimia* showed lower MICs, and *Cunninghamella* and *Mucor* exhibited a higher range, thus concluding that itraconazole may be useful wherever strains are susceptible. (29)

***Terbinafine***

Mucormycetes demonstrate a wide range of MIC for Terbinafine as has been shown by Dannaoui et al. His results demonstrated that terbinafine was active against isolates of *Rhizopus microsporus and Lichtheimia corymbifera*, some *Rhizopus* and *Mucor* isolate whereas *Rhizopus arrhizus* was resistant. (29)

***Echinocandins***

In vitro studies have suggested minimal activity of caspofungin against Mucormycetes. A study has suggested synergism between caspofungin (1 mg/kg/day) plus amphotericin B lipid complex (5 mg/kg/day), however, more studies are needed to prove the hypothesis. (6)

**C. Adjunctive Therapy**

***Hyperbaric Oxygen***

Hyperbaric oxygen acts as an adjunctive therapy by aiding in fungal killing or diminishing its growth rate, thus recovering the host immune reaction. It may act by improving neutrophils activity and its growth-suppressive effects on the fungal spores and mycelium. This modality is known to improve the overall survival of the patient. (5)

***Iron Chelators***

Iron chelators such as desferrioxamine increase the risk of Rhizopus infection. However, some iron chelators like deferasirox inhibit the iron uptake by Mucormycetes and so are used in long-term blood transfusion patients with chronic iron overload as adjunctive agents. (33)

Mucormycosis is a deadly disease with high mortality. This disease must be suspected and treated as early as possible to be able to contain it at an earlier stage. Efforts should be made to control the predisposing factors like diabetes mellitus which increase the risk of this deadly disease.

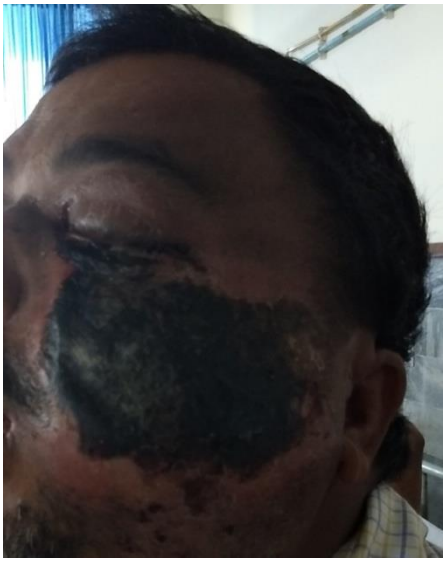

**Fig 1**: Case of Rhinoorbital Mucormycosis with swelling of left cheek and eye and blackening of left cheek

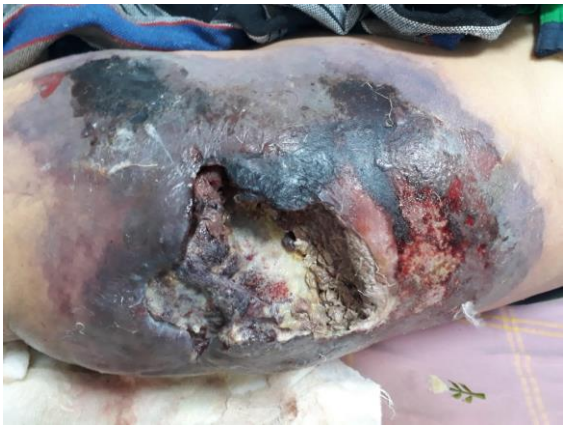

**Fig 2**: Case of Cutaneous Mucormycosis with involvement of left buttock area post intramuscular injection

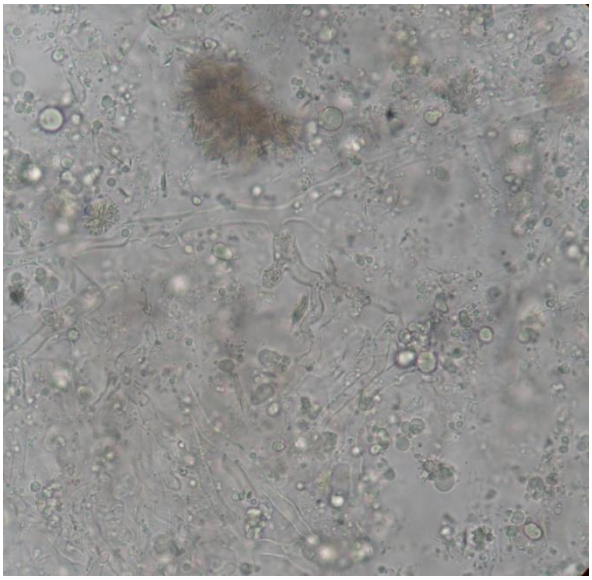

**Fig 3**: Broad aseptate hyphae with right angle branching seen on KOH mount at 400X magnification

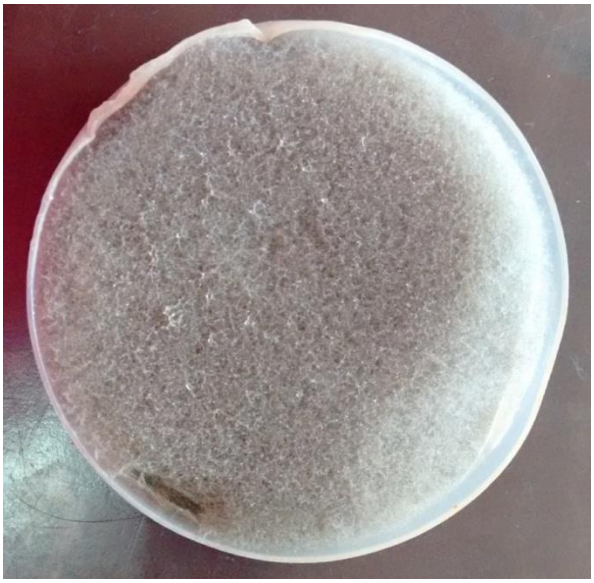

**Fig 4**: Rapidly growing wooly colony of *Rhizopus arrhizus* turning brownish-black occupying the whole plate after 48 hours of incubation

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