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Pathophysiology of Mucormycosis

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Abstract: *Mucormycosis is an angio invasive infection that occurs due to the fungi mucorales. It is a rare disease but increasingly recognized in immunocompromised patients. It can be categorized into rhino-orbito-cerebral, cutaneous, disseminated, gastrointestinal, and pulmonary types. Overall increased mortality rate is reported, even though the aggressive treatment is given. The main aim and purpose of this review related to overview and Eopathogenesis of Mucormycosis, fatality of rhinocerebral Mucormycosis, recent advances in diagnosic and treatment methods.*

Background: Mucormycosis is an infection give rise by a group of filamentous molds belong to order Mucorales and class Zygomycetes. Mucormycosis is often known as black fungus disease. This infection mainly targets diabetic and immunecompromised patients. As COVID-19 infection declines the immunity of patients, somucormycosis cases are also increasing due to inhalation of molds containing industrial oxygen.

Objective: The main aim of the present article is to provide a comprehensive review on mucormycosis, its epidemiology, pathophysiology, diagnosis, treatment, and its association with COVID-19.

Methods: We searched the electronic database of PubMed and Google Scholar from inception until May 13, 2021 using keywords. We retrieved all the granular details of case reports/series of patients with mucormycosis, and COVID-19 reported world-wide. Subsequently we analyzed the patient characteristics, associated comorbidities, location of mucormycosis, use of steroids and its outcome in people with COVID-19.An extensive literature search were carried out in various search engine like PubMed, Google Scholars, Research Gate by using the keywords like Mucormycosis, Black fungus, Mucorales, Zygomycetes, Rhizopus, etc. Between period of March, 2021 To June 2021.

Keywords: Mucormycosis**,** Black Fungus, Mucorales, Diabetes mellitus (DM), COVID, Glucocorticoids, Rhizopus, ROCM

I. INTRODUCTION

Mucormycosis is antimeserving expedient fungal infection caused by fungi of order Mucorales which includes multiple subdivision including Rhizopus, Rhizomucor, Mucor, Actinomucor, and Lichtheimia (formerly Absidia), etc. This is highly invasive and relentlessly progressive, resulting in higher rates of morbidity and mortality. These fungi are a common commensal in healthy individuals and cause infection primarily in immunocompromised patients with uncontrolled diabetes defects in phagocytic function (neutropeniaorglucocorticoid treatment), and/or elevated free iron level (supports fungal growth). The approximate prevalence of mucormycosis is around 70 times higher in India than that in global data.[**1]** However, during the second wave of COVID-19 pandemic in India, there is surge of rhino-orbito-cerebral mucormycosis (ROCM) cases which has made India the highest burden of mucormycosis instances.[**2]** Multiple risk factors including overuse of steroids, poor control of hyperglycemia, ketoacidosis, increased serum-free iron (due to hyperferritinemia and acidosis) , and lymphopenia (reflected in high neutrophil-lymphocyte ratio, NLR) are classical risk factors. Along with these, careless use of multiple antibiotics, overuse of zinc supplements, and poor mask hygiene are being suspected as possible risk factors but the exact cause is yet to come forward. The unique nature of COVID-associated mucormycosis (CAM) cases is a predilection to rhino-orbital involvement. Whether COVID-19 infection is an independent risk factor of ROCM is a valid research question to be answered in the future.[**3]**The progressive nature of ROCM needs to be managed promptly with great concern as delay in appropriate management leads to worse outcome. Hence early diagnosis and treatment with a multidisciplinary team are necessary consisting of

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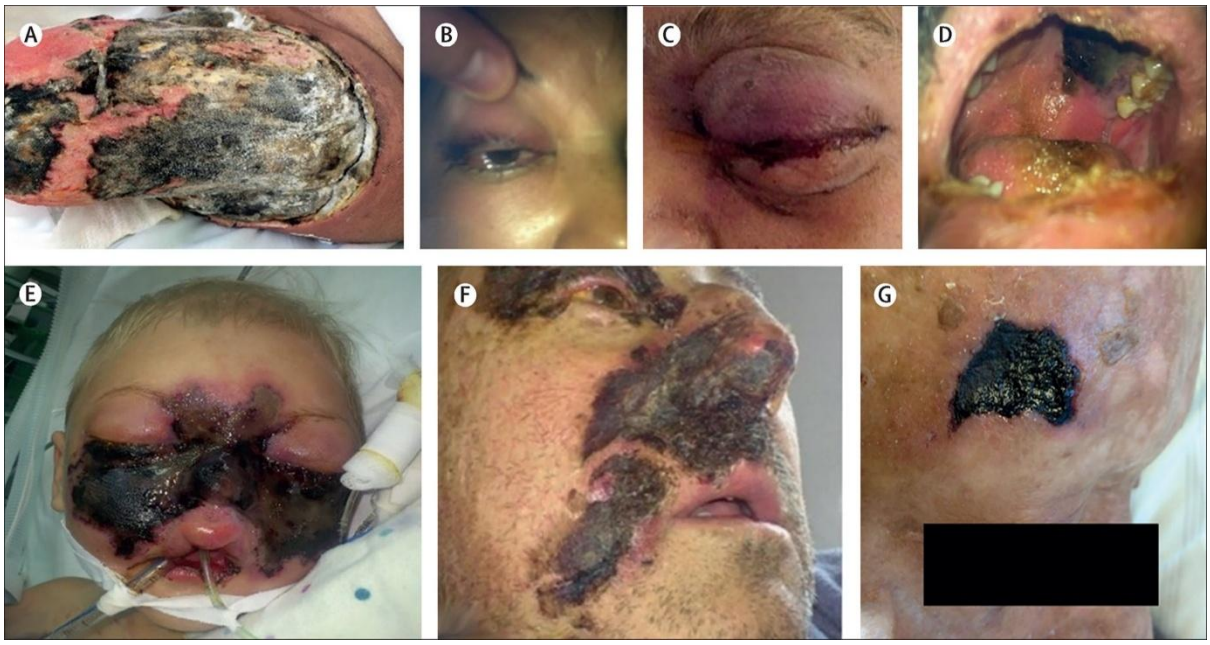
experts in the diagnostic field (microbiology, pathology, radiology), medical (internal medicine, neuro-medicine, critical care), and surgical (otorhinolaryngology, ophthalmology, neurosurgery) care.[**5,6]**



History:

In 1885, the German pathologist Paltauf, reported the first case of Mucormycosis and described it as Mycosis Mucorina[**4**]. During 1980s and 1990s Mucormycosis was increasingly seen among immuno compromised individuals[**7].**Based on the prevalence rate, a study carried out in France reported amplification by 7.4% per year4. Globally occurrence along with the possibility of seasonal variation of mucorales infection has been noted[**8].**

EPIDEMIOLOGY

The chances of occurring mucormycosis is very frequent but from last two decades the cases of this disease increase abruptly particularly in Belgium, France, Switzerland and India **[9,10,11-13]**. According to a announce from National Hospital Discharge Database, France identified 35,876 patients with invasive fungal infection (IFIs) were catched in between 2001 to 2010; among which 1.5% of IFIs instance were of mucormycosis itself **[11]**. 19 cases of mucormycosis were identified in a single-center learning in Spain from 2007 to 2015. Likewise, in a tertiary hospital; from Geneva, Switzerland, within 1989 to 2003; 3 cases of mucormycosis were identified while 16 cases were found in between 2003 to 2008 **[13,14]**. It was discovered that, people with medication of immunosuppressive drug and voriconazole were more susceptible to infection of black fungus **[13]**.

PATHOPHYSIOLOGY:

Sporangiospore ingestion or inhalation or inoculation of bacterium via wounds or trauma, inhalation of saturated oxygen, medical equipment or improper airing out system are the ways through which black fungus got inside of a patient **[10,16,17]**. Scavenger cell plays an important role in infection of Mucorales. The mycelium and spores of molds which cause mucormycosis can be easily countered by mononuclear or polymorphonuclear phagocytes. Therefore, persons with very low number of phagocytes or disabled phagocytosis function are at greater risk of black function infections**[18]**. Excessive chemotherapy can lead to development of leukopenia which become a soft target for this mucormycosis. Along with this, patient with defective neutrophil function due to poor controlled of blood sugar level, acidic pH and ketoacidosis hyperglycemia can acutely damage motility and phagocytic capacity of neutrophil **[19]**. Moreover, phagocytic work can also be compromised by over-dose of glucocorticoids due to which they will not be able to kill the ingested Mucorales **[15]**.The metabolism of iron plays a significant role in pathogenesis of mucormycosis **[22,16,20,21]**. Mucormycosis have the capacity to extract iron from host for their survival and

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multiplication as well as to perform various enzymatic activities. Rhizopus oryzae was used for identification of iron sequester activity and it was found that, mucormycosis grow fastly in iron containing media but very poor growth in serum devoid of iron **[23]**. Studies revealed that, iron chelator are acts as inhibitor to growth of Rhizopus by capturing free iron while some others act as siderophore by transferring iron to fungal cell for their growth, therefore, patient with iron treatment such as deferoxamine for iron overload are more prone to get infected by mucormycosis**[24]**. Bacteria or fungi used to produce a low molecular weightmolecule called Siderophores which have strong affinity and specificity to chelate iron molecules. Deferoxamine is a siderophore produce by fungi which have strong affinity for iron and they can isolate iron from ferritin and transferrin to used them for living inside host**[25]**. During intracellular transport, Rhizopus use deferoxamineas iron source by induce a receptorwhich further trap deferoxamine-iron complexes and to inhibit the conversion of ferric to ferrous iron**[15]**. Mucormycosis have a specific mode of action to invade the endothelial cells from vascular system due to which infection got disseminated from one to other parts of the body. During glucose starvation, GRP78 receptors on cell surface got upregulated and acts as receptors for Mucorales in human to diminished the endothelial cells **[26]**.

II. CLINICAL MANIFESTATION OF MUCORMYCOSIS- TYPE, SIGN AND SYMPTOMS:

Forms of Mucormycosis	Pathogenesis of disease state	Underlying host risk factor	Clinical manifestations	Mortality rate	References
Rhino-orbital-cerebral	Inhalation of sporangiospores grow paranasal sinuses which can further spread to involve sphenoid sinus, cavernous sinus and brain tissue	Malignancy,Diabetes mellitus, body part transplant	Sinusitis, eye/facial pain, facial numbness, blurry vision, proptosis, headache	50% or may be higher depends on concentration of immunosuppression	[27,28]
Pulmonary	Pulmonary blood vessel got invaded by hyphae which can further result in hemorrhage, ischemia, thrombosis, infarction of distal tissue	Under chemotherapy, neutropenia, lung transplantation	Prolonged fever, nonproductive cough, endobronchial lesion result in inhibition in airway	66% or higher depend on level of immunosuppression	[29-31]
Cutaneous	Due to direct inoculation of spores into the skin which can further lead to disseminated disease, but chances are very less to occur from internal organ to dermis	Trauma/ burn of skin in susceptible host	Gradual onset to invasive one, fulminant disease, can lead to gangrene and hematogenous dissemination	Varies with severity of disease, 25%	[32]
Gastrointestinal	By ingestion of contaminated milk, porridge, breads, alcoholic drinks,	Malnourished children, diabetes mellitus,	Appendiceal, gastric, cecal, gastric perforation,	85%	[33]

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	herbal and homeopathic formulationbecause of stomach and colon get affected	premature baby, immunosuppresion.	neutropenic sufferer with fever, typhlitis and hematochezia		
Disseminated	Mucormycosis from one organ can transferred to other organ through blood, lungs infection is most widely happening with dissemination	Iron overload, excessive	Depend on the site of infection and intensity of capture	Can be fatal if disadvantage of medication	[16,49]
Miscellaneous	Mycosis /contaminated medical instruments, Mucorales impured food stuff such as barley, wheat, onions, cottons, sweet potatoes, oranges, honey and tomatoes	Traumatic infuse during surgery, contaminated medical devices (catheters, adhesive tapes), immunosuppres sive patients	Disease of skin, prosthetic valve endocarditis, osteomyelitis, peritonitis, gastrointestinal disease	Be conditioned on site of infection and immunocompromised host	[35]

Diagnosis:

Diagnosis of mucormycosis includes careful evaluation of clinical manifestations, magnetic resonance imaging modalities, utilization of the computed tomography (CT) in the premature stages, specialist assessment of cytological & histological provision, finest application of clinical microbiological technique & execution of molecular detection**[36]**. Detection of host elementscontribute extensively to the estimation of the patient's possibility for invasive mucormycosis. PAS stains, direct examination, calcofluor, histopathological examination, Gomori methane amine silver stain, culture, molecular methods and bright in situ hybridization are the various laboratory techniques for detecting mucor**[36]**. In accordance with Kontoyiannis et al., the major issue in the identification of mucormycosis includes its indefinable clinical appearance and recurrent occult distribution, & hence a need for a reactive nonculture-based investigative method is required. Gold standard analytic technique for proof is the tissue based analysis**[38]**.

Differential Diagnosis

Differential finding of mucormycosis include maxillary sinus neoplasia, maxillary sinus aspergillosis, soft tissue infarction, soft tissue radio necrosis, other deep fungal inanalysis [**37]**.

Prevention:

It is important to note that although these activity are recommended, they haven't been proven to prevent mucormycosis.**[43,44]**

Try to keep away from areas with a lot of dust like construction or excavation sites. If you can't avoid these places, wear an N95 mask (a type of face mask) while you're there

• Avoid direct contact with the water-damaged buildings and overflow of water after hurricanes and natural disasters. **[45]**

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• Avoid activities that require lose contact to soil or dust, such as yard work & gardening. If this isn't possible,
• Wear shoes, long pants, and a long-sleeved shirt when performing out side door activities such as gardening, visiting wooded areas.
• Have on hand gloves when handling materials such as soil, moss, or manure.
• To minimize a chances of developing a skin infection, clean skin injuries well with soap & water, especially if they have been uncover from to soil or dust.
• Antifungal medication. Assume If you are at high chance for developing mucormycosis (for example, if you've had an stem cell transplant), your healthcare provider may advise medication to prevent mucormycosis & other mold infections. **[46,47]** Doctors & scientists are still studying about which transplant patients are at highest risk and how to best stop fungal infections

Treatment

Prosperous treatment for mucormycosis includes rapid accurate diagnosis, surgical debridement, & administration of drugs, adjunctive application of the recompression oxygen, recombinant cytokines or transfusion of granulocyte and prosthetic obturator**[39,41]**.According to Spellberg et al., currently available monotherapy shows elevated mortality rate especially with haematology patients and hence proposed the choice of "Combination therapy" for Mucormycosis**[39]**. Antifungal therapies involvesAmB Dexycholate, Liposomal AmB (5-10mg/kg), AmB lipid complex, AmB colloidal dispersion, Posaconazole (400mg bid) and manage of core conditions. Second-line therapy includes combination of caspofungin and lipid AmB, mixture of lipid AmB and Posaconazole, not grouping with Deferasirox is suggested**[40]**.
In case of soft tissues, cerebral disseminated, localized pulmonary lesion & rhino-orbito- types surgical treatment should be think about.**[40].**

III. CONCLUSION

In conclusion, Mucormycosis is a life-threatening infection that most commonly affects immuno compromised individuals & that despite aggressive multimodal treatment carries a significant risk of mortality. A high index of the suspicion is essential in order to begin the appropriate diagnostic workup and treatment. Our cases most commonly includes the rhino-orbital cerebral cavities, and the main underlying disease was DM. Unluckily due to the economic limitations, the use of liposomal amphotericin B in third world countries are frequently prohibitive, & our patients were instead treated with the conventional amphotericin B. Fortunately, there were no instances our series where side effects (such as renal injury or hypokalemia) forced a change in a therapy. In light of proof suggesting that early & aggressive use of the liposomal amphotericin B could develop outcomes **[42]**, this issue should be evaluated thoroughly.

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