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REVIEW ARTICLE **OPEN ACCESS**

Mucormycosis: A Review and Update

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ABSTRACT
Mucormycosis is an angio-invasive infection and has drastically boomed in previous couple years, caused principally by fungi of order Mucorals. These particular fungi have a tendency to invade artery walls, resulting in widespread emboli and necrosis in many organs, creating variable clinical characteristics. Classical mucormycosis histology and culture, together with molecular testing, are still most relevant procedure for the demonstration of fungal hyphae. This review study adds to our understanding of mucormycosis's microbiology, clinicopathogenesis, and effective screening methods.
Keywords: *COVID-19-associated mucormycosis, Receptor glucose- regulator protein 78, Grocott methenamine-silver, Amphotericin B*

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INTRODUCTION

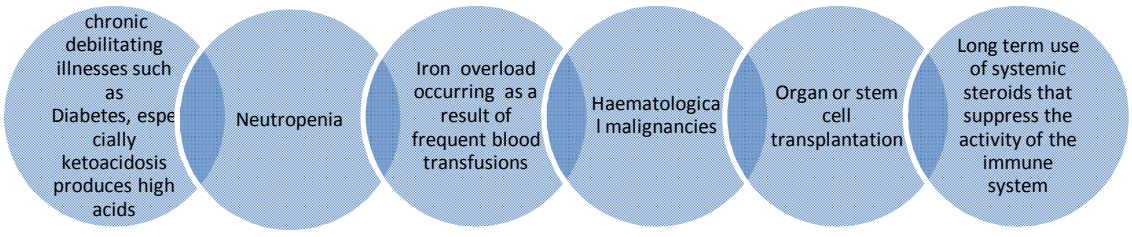
Mucormycosis is a rare, frequently aggressive, devastating angio-invasive infection which is life-threatening condition that poses a serious risk of death and high morbidity and mortality typically affects people with immune system issues. Moreover, it's caused by fungi- Zygomycetes comprised of the orders Mucorales and Entomophthorales [1].

In humans, the illness is spread particularly through inhaling sporangiospores, although it can also be disseminated by eating infected food or receiving a traumatic injection. If untreated, they have a propensity for migrating into arteries and lymphatic's, where they cause the development of microscopic thrombi, tissue ischemia including infarction, which can be lethal.[2] Worldwide, the incidence rate of mucormycosis varies between 0.005 and 1.7 per million individuals.[3] In the second wave of COVID-19 which was considered to be crucial, 28 states in India documented 28,241 cases of mucormycosis. Also, there are 24,350 individuals with a history of COVID-19 and 17,602 cases with a history of diabetes. It is often referred to as the 'Black fungus' which is a misnomer till now. It's so called because it produced tissue necrosis and subsequently decomposition the lesion result in eschar which gives the appearance of coloured black [2].

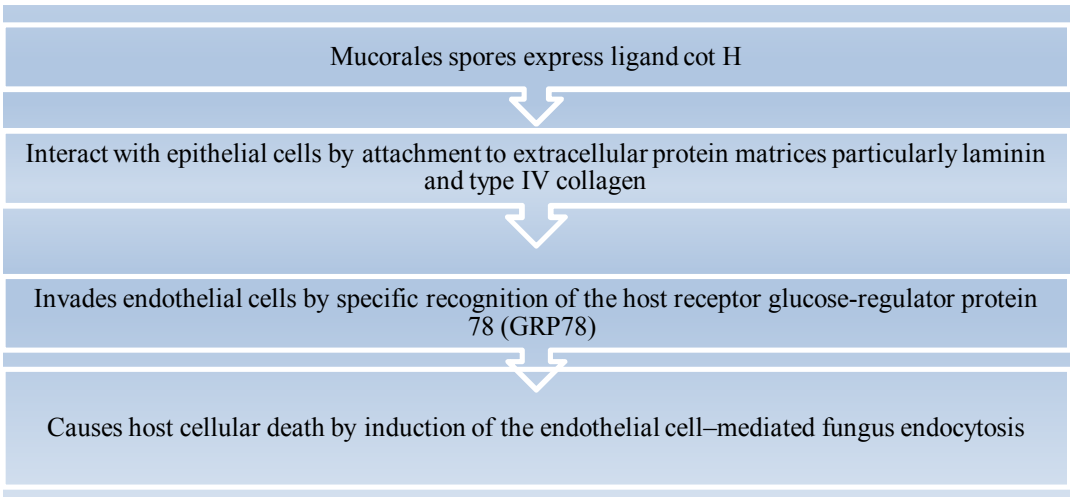
HISTORY

In 1885, German pathologist Paltauf, documented the first case of mucormycosis in humans and coined term 'Mycosis Mucorina'. However, later described a case of upper pulmonary mucormycosis within the Virchows archives of pathology and anatomy under the title "mucormycosis mucorina." An American pathologist, R. D. Baker coined it's name which is used nowadays as "mucormycosis [3-4].

RISK GROUPS [5]

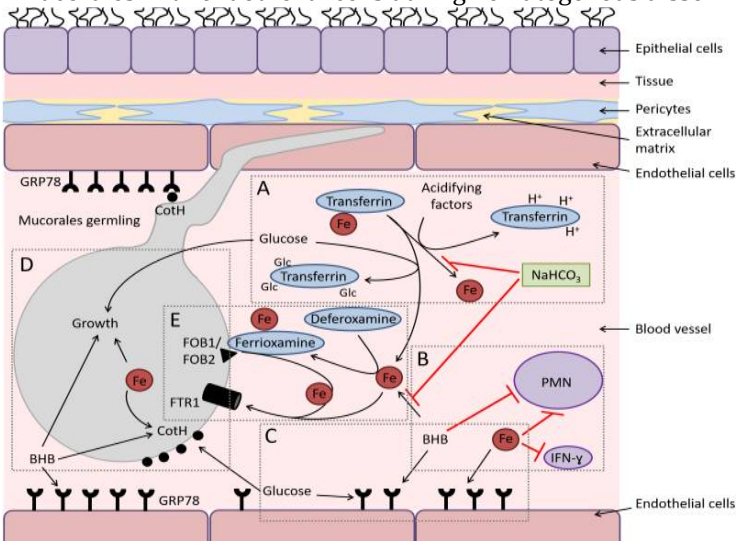


PATHOGENESIS



Unique receptors allow for the invasion within the endothelium, thus escalating the disease's aggressiveness [6]. The tissue microenvironment is changed in diabetes patients, and the presence of high amounts of glucose, free iron, and ketone bodies facilitates the development of the fungus [7].

Figure 1: Mucorales with endothelial cells during hematogenous dissemination



CLINICAL FORMS OF MUCORMYCOSIS

Based on its clinical signs and anatomical region of involvement, mucormycosis is differentiated into various forms.

(1) Rhino Ocular Cerebral Mucormycosis (ROCM)

The most prevalent type of mucormycosis is rhino ocular cerebral mucormycosis particularly seen in patients with diabetic ketoacidosis or uncontrolled diabetes mellitus. In majority of the cases, ocular indications are caused when the mucor penetrates the pterygo-palatine fossa, inferior orbital fissure and ultimately the retroglobal portion of the orbit [8].

Table 1. Clinical presentation

Clinical presentation	
(a) Ophthalmic signs and symptom	Eye pain, decreased vision, ophthalmoplegia, proptosis, ptosis, chemosis, orbital cellulitis periorbital discolouration and necrosis
(b) Non-ophthalmic symptom	Fever, headache, facial pain, facial swelling, nasal ulceration, nasal discharge, epistaxis, sinusitis, hemiplegia, seventh cranial nerve palsy, tooth ache [9]

Clinical Progression

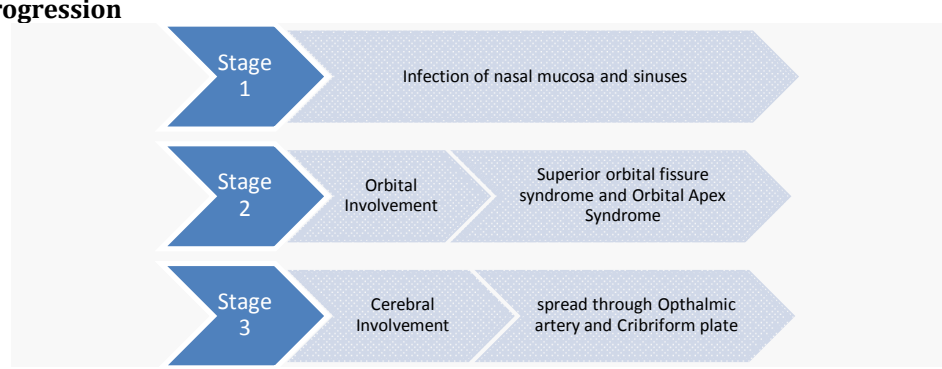


Figure 2: Eyelid swelling, axial proptosis with eyelid necrosis.

(2) Pulmonary Mucormycosis

Hematogenous or lymphatic spread as well as ingestion of sporangiospores are two ways that can originate this form of mucormycosis. The best technique for evaluating the degree of pulmonary mucormycosis in Computed tomography is the typical reverse halo sign appreciated in the early stages of the illness [10].

(3) Cutaneous Mucormycosis

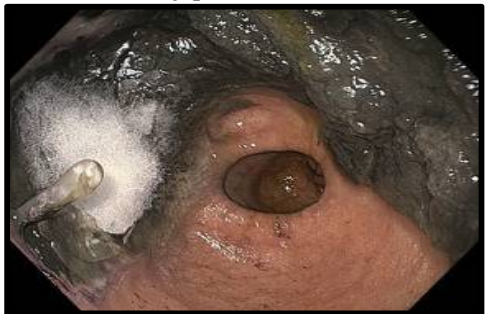
The third most prevalent kind of mucormycosis, primary cutaneous mucormycosis (PCM) originates following a breach in the skin.It often spreads nosocomially and frequently attacks the extremities in immunocompromised patients. Most often it affects the skin along with gut in children than in adults. An erythematous and indurated patch of skin encircled by a necrotic scar is a typical presenting feature of such form [11].

(4) Gastrointestinal Mucormycosis

Only 8% of cases of mucormycosis occur in the gastrointestinal tract, making it a rare type of the infection. It is frequently encountered in low birth weight babies, impoverished individuals on peritoneal dialysis, HIV patients, organ transplant recipients and those with Systemic lupus erythematosus [12].

Figure 3: Necrotic ulcer

Figure 4: Black eschar with white cottony pseudomembranous mucosa in prepyloric region.



(5) Disseminated Mucormycosis

Mucormycetes may infect any organ in the human body and can propagate there, although they most regularly infect the lungs. Patients on immunosuppressants and antifungal prophylaxis (especially voriconazole) are more likely to acquired these type of infection. If the brain is affected, convulsions, stroke, paralyzed, and abscess development result. Its mortality rate is much higher [13].

DIAGNOSIS

Nowadays, mucormycosis challenging to diagnose in the lab because quick and fulminating course of the disease which are frequently encountered as laboratory contaminants. Therefore, tissue-based analysis is the evaluation is the gold standard technique for assessment [14].

(1) Radiodiagnosis

The diagnosis of invasive fungal infections includes CT and MRI scans, which should be performed quickly once if mucormycosis is suspected since they benefit in early recognition. Iso-dense lesions, a rim of soft tissue thickness along the paranasal sinuses, full sinus opacification, and air-fluid levels can all be seen on a CT scan which is peculiar for rhinocerebral mucormycosis. Initially, a powerful indicator of pulmonary mucormycosis is the halo sign on CT which suggests a localised consolidation with nearby ground-glass opacity reflecting vascular and chest wall invasion. Thereafter, the reversed-halo sign must be recognized appropriately [15].

(2) Laboratory Diagnosis

(a) Direct Microscopy

With wet KOH, direct microscopy is used to immediately for presumptive diagnose of mucormycosis and enhanced the visualization of the distinctive fungal hyphae in tissue samples of afflicted areas. Fluorscent brightners such as Blankophor and Calcoflour White combined with KOH enhances the distinguishing hyphae visualized under fluorescent microscope. They exhibit broad, non-septate, ribbon-like hyphae with wide-angle or right-angle branching at uneven intervals [16].

(b) On Histological Examination

For the most cases hematoxylin and eosin (H&E) stain is principally used for demonstrating of hyphae although there are also specific stains like Grocott methenamine-silver (GMS) and periodic acid-Schiff that can also help to high lightening the fungal wall [17].

Mucorales genera often produce typical ribbon-like hyphae with usually no or few septations characterized by non-pigmented, pale-staining, broad (approx. 5–20 μm) with branching at right-angle, unlike those of *Aspergillus* species or other hyaline moulds, which are generally 3-5 m broad, septate, and create acute-angle branching. Sample for cytologic inspection can be received through needle aspiration cytology or scrape smears [18].

Figure 5: Mucorales hyphae & spores.

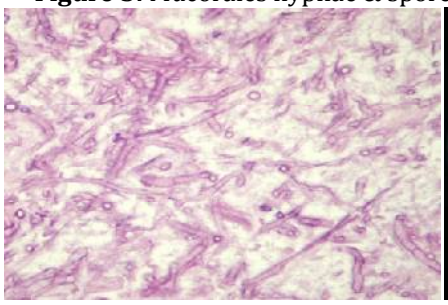


Figure 6: fungal structures.

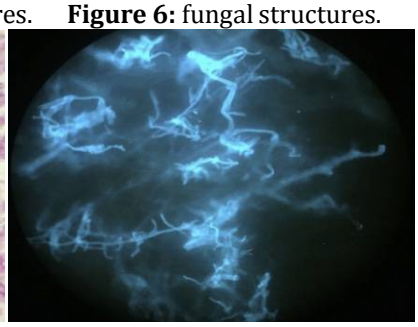


Figure 7: silver stained mucosa highlighting fungal elements.

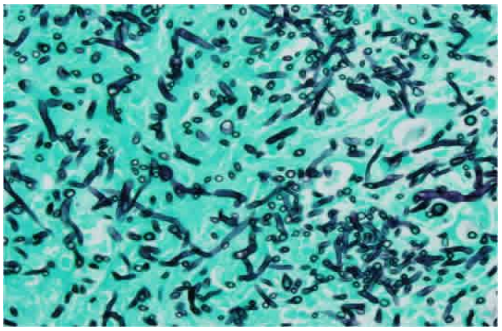
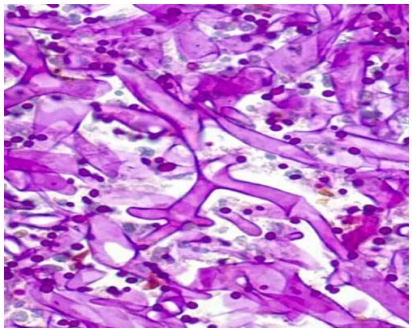


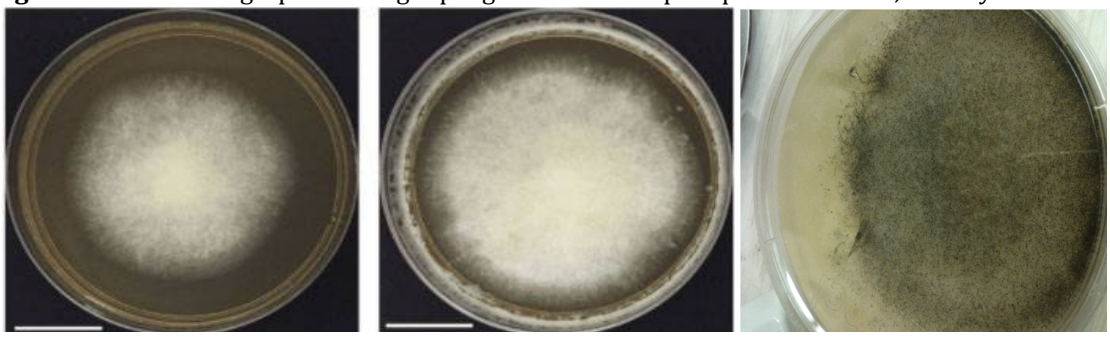
Figure 8: nonseptate fungal hyphae with branch



(c) Culture

On any carbohydrate medium, these may grow much faster at 37°C, and colonies can form in approximately 24-48 hours. One of the most essential feature is that the specimen should be promptly inoculated on culture media without being subjected to grinding or homogenization, which might harm the fragile hyphae of mucormycetes. The mycelial colonies expand as white, floccose, packed and have hairy presentation and mycelia are depicted as fibrous or cotton-candy growth, which is very vigorous hence some are considered as 'lid-lifters'[19].

Figure 9: Photomicrograph showing rapid growth of Rhizopus species as white, cottony colonies



Recent advances such as Matrix Assisted Laser desorption ionization - with little study on precise diagnosis. Moreover, a number of molecular assays including as Real time (qPCR), PCR combined with electrospray ionization mass spectrometry (PCR/ESI-MS) have been effectively targeted the 18 s ribosomal RNA genes [20].

CONCLUSION

The first line of drug for the treatment of mucormycosis is liposomal derivative of amphotericin B, which generates minimal nephrotoxicity and contributes to even higher dosages of 5–15 mg/kg/day. Other antifungals like posaconazole or isavuconazolehave are a new category of extended range of triazole certified for the treating mucormycosis. For localized forms of mucormycosis, surgical debridement of necrotizing tissue and septic tissue is supreme procedure for the controlling its extension. Hyperbaric oxygen therapy helps in revascularization of the necrotic or ischemic [21].

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