Management of mucormycosis

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Abstract: A zygomycete family opportunistic fungal infection called mucormycosis can result in a variety of illness. The majority of the time, the hosts have underlying problems that make them more susceptible to infection. Mortality increases noticeably, approaching 70–90% in cases of disseminated mucormycosis, depending on patient features (such as those of critically ill or immunocompromised individuals) and site of infection. In India, isolated renal mucormycosis has developed as a new clinical entity, and rhino-orbito-cerebral presentation accompanied with uncontrolled DM was the prevalent feature. Black fungus can enter a patient's body through sporangiospore ingestion, inhalation, or inoculation via wounds or trauma, inhalation of saturated oxygen, medical equipment, or an inadequate ventilation system.

Keywords: mucormycosis, zygomycete, fungal infection, rhino-orbito-cerebral, epidemiology

Introduction
A zygomycete family opportunistic fungal infection called mucormycosis can result in a variety of illness. The majority of the time, the hosts have underlying problems that make them more susceptible to infection. Due to the fact that the causative fungus are common environmental organisms, immunocompetent people typically do not develop any symptoms.[1] It can affect immunocompetent hosts as well (such as trauma patients), despite the fact that it is typically classified as an opportunistic infection that preferentially affects people with diabetes mellitus (DM), neutropenia, malignancy, chronic renal failure, and acquired immunodeficiency syndrome. It also affects people who have had organ or hematopoietic stem cell transplants.[2][3]

Overall mucormycosis infection mortality is still high, ranging from 20 to 50%, despite rigorous surgical and polyene antifungal therapy. Mortality increases noticeably, approaching 70–90% in cases of disseminated mucormycosis, depending on patient features (such as those of critically ill or immunocompromised individuals) and site of infection. [4][5]

According to a recent projection for the years 2019-2020, mucormycosis prevalence ranged from 0.005 to 1.7 per million people worldwide, but in India, it is approximately 80 times higher (0.14 per 1000) than in wealthy nations [[6],[7], [8]]. To put it another way, India has the highest rate of mucormycosis in the entire world. Nevertheless, India was previously the world's diabetes capital and has the second-highest prevalence of diabetes mellitus (DM) in the world.[9]

Etiology
Mucor spp., Rhizopus spp., and Lichtheimia spp. (formerly Absidia and Mycocladus) spp. are the three most prevalent mucormycosis-causing organisms.[10] Uncontrolled diabetes mellitus, in particular ketoacidosis, steroid use, extreme ages, neutropenia, particularly with haematological malignancies, AIDS, renal failure, organ or stem cell transplantation, iron overload, skin trauma, broad-spectrum antibiotics, intravenous drug abuse, prophylactic voriconazole for aspergillosis, and malnutrition are risk factors.[11]

There are significant regional variations in the aetiology of mucormycosis. For instance, the most typical fungi found in mucormycosis patients in Europe were Rhizopus spp. (34%), Mucor spp. (19%), and Lichtheimia spp. (19%).[12] Apophysomyces elegans, A. variabilis, and Rhizopus homothallicus are emerging species in India, where Rhizopus species are the most frequent causes of the disease. Uncommon agents like Mucor irregularis and Thamnostylum lucknowense are also being documented.[13] [14] Mucormycosis is an infection caused by fungi belonging to the order Mucorales.[15] Due to lengthy hospital stays, a lack of medical personnel, and ensuing aseptic settings, the current COVID-19 pandemic scenario presents additional potential for disease entrance. In order to give oxygen to hypoxic patients, mechanical ventilators have been identified as the most usual entrance point.[16]

Epidemiology
The majority of human infections are brought on by direct inoculation of organisms into damaged skin or mucosa or by inhalation of fungal sporangiospores that have been discharged into the air.[17] The Mucorales are widely distributed in nature, however it is unclear exactly what their ecology involves. They are thermotolerant and typically found in decomposing organic debris. There may be seasonal change in Mucorales infection.[18]

Between developed and developing nations, mucormycosis epidemiology appears to differ. The condition is still rare in wealthy nations and is now most common in people with diabetes mellitus, haematological malignancies (HMs), who are receiving chemotherapy, and people who have had allogeneic stem cell transplants.[19] The primary clinical manifestation of the disease in HM patients is pulmonary. [12, 20] In India, isolated renal mucormycosis has developed as a new clinical entity, and rhino-orbito-cerebral presentation accompanied with uncontrolled DM was the prevalent feature. The primary clinical manifestation of the disease in HM patients is pulmonary.[13] In a significant Mexican study that looked at 418 instances, diabetes was the underlying condition in 72% of patients and was linked to sinusitis. In the group of patients who had underlying malignancies, the pulmonary and sinus presentations were identical. [21]

Pathophysiology
Black fungus can enter a patient's body through sporangiospore ingestion, inhalation, or inoculation via wounds or trauma, inhalation of saturated oxygen, medical equipment, or an inadequate ventilation system.[22,23,24] An key part of Mucorales infection is played by phagocytes. Mononuclear or polymorphonuclear phagocytes can effectively combat the hyphae and spores of moulds that cause mucormycosis. Therefore, individuals with a very low phagocyte count or defective phagocytosis function are...
more likely to contract black function infections.[25] Patients with severe neutropenia and those without phagocytic function are more likely to develop mucormycosis. However, it differs for AIDS patients.[26] Phagocytes are dysfunctional in the presence of hyperglycemia and low pH, which is seen in individuals with diabetic ketoacidosis (DKA), and they exhibit poor chemotaxis and defective intracellular death by both oxidative and nonoxidative processes.[27] Mucormycosis can absorb iron from the host for survival and reproduction as well as to carry out a variety of enzymatic functions. When using Rhizopus oryzae to test iron sequester activity, it was discovered that mucormycosis grows quickly in media containing iron but extremely poorly in serum devoid of iron.[28] Siderophores, which have a significant affinity and specificity to chelate iron molecules, are a low molecular weight molecule that are produced by bacteria or fungus. Fungi that have a significant affinity for iron can and will separate it from ferritin and transferrin to use for life inside hosts create the siderophore deferoxamine.[29] Because of a unique mechanism used by mucormycosis to penetrate vascular endothelial cells, the infection spread from one area of the body to another. GRP78 receptors on cell surfaces became more active during glucose deprivation, acting as receptors for Mucorales in humans to kill endothelial cells.[30]

**Clinical manifestation**

Tissue necrosis caused by angioinvasion and subsequent thrombosis is the clinical hallmark of invasive mucormycosis. The infection usually progresses quickly and kills the patient unless the underlying risk factors (such as metabolic acidosis) are treated, antifungal medications are used aggressively, and surgical excision is performed. Invasive mucormycosis is divided into one of the six main clinical variants based on the anatomic site and clinical presentation: Rhinocerebral, pulmonary, cutaneous, gastrointestinal, disseminated, and six unusual, rare types, including endocarditis, osteomyelitis, peritonitis, and renal infection[31,32,33] Roden et al. evaluated 929 cases of mucormycosis and discovered that the most frequent sites of involvement were the sinuses (39%), lungs (24%), disseminated (23%) and skin and soft tissue infection (SSTI) (19%). In a different study, among 154 cancer patients, 92 (60%) had lung disease, and 6 (4%) had ROCM.[34]

**Diagnosis**

It is crucial to diagnose mucormycosis as soon as possible because doing so may improve the prognosis. Studies have revealed that it improves survival rates[35], and it may also lessen suffering, deformity, or the necessity for surgical resection. The best use of clinical microbiological technique, execution of molecular detection, expert assessment of cytological and histological data, utilisation of computed tomography (CT) in the early stages, and careful evaluation of clinical manifestations are all necessary for the diagnosis of mucormycosis.[36] Higher resolution computed tomography (CT) and magnetic resonance imaging can be very helpful for the diagnosis of pulmonary, rhino-orbital-cerebral, and disseminated mucormycosis.[37]. Eight patients with pulmonary mucormycosis had wedge-shaped consolidation or nodules on CT chest imaging, mostly in the posterior regions of the upper lobes of the lungs, but there were relatively few endobronchial lesions seen.[38] Histopathological evaluation and culture are reliable methods for determining whether someone has mucormycosis.[39,40] A black eschar or dead tissue may be visible on infected individuals with mucormycosis as a result of tissue infraction and blood vessel thrombosis.[41] Quantitative PCR in tissue or serum can be used to diagnose some species, such as Mucor, Rhizomucor, Rhizopus, and Lichtheimia, and it may be more effective than culture approach.[39,42-50]

**Management of mucormycosis**

The essential factor in controlling mucormycosis is early diagnosis. Early and prompt diagnosis is crucial for the efficacy of therapies, as is the elimination of risk factors for mucormycosis[51] Intravenous (IV) amphotericin B (lipid formulation) is the drug of choice for initial therapy.[52,53] For individuals who have responded to amphotericin B, step-down therapy may involve the use of posaconazole or isavuconazole. For patients who don't respond to or are unable to tolerate amphotericin B, posaconazole or isavuconazole can also be used as salvage therapy; whether to use oral or IV posaconazole or isavuconazole for salvage therapy depends on the severity of the patient's illness, whether an initial course of amphotericin B could be given, and whether the patient has a healthy gastrointestinal (GI) tract.[56,57]

Surgery- A different approach of treating mucormycosis, particularly when soft tissue or the rhino-cerebral region is involved, is surgical debridement of the affected tissue.[54,55] As soon as a diagnosis of any type of mucormycosis is suspected, aggressive surgical debridement of the affected tissues should be taken into consideration. In anecdotal clinical assessments of rhinocerebral and pulmonary infection, surgical intervention with removal of necrotic tissue and debulking infection has been linked to better survival.[56,57] Debridement to remove all necrotic tissue in the case of a rhinocerebral infection can frequently be disfiguring and necessitate the removal of the orbit, palate, and nasal cartilage. But more recent research demonstrates that endoscopic debridement with minimal tissue removal is possible.[57]

Mucormycosis infection outcomes are improved by the early start of antifungal medication. This was demonstrated in a retrospective analysis of 70 patients with hematologic malignancies who also had mucormycosis, in which the mortality rate at 12 weeks following diagnosis increased by almost a factor of two due to delayed amphotericin B therapy (beginning treatment 6 days after diagnosis) (83 versus 49 percent).[58]

Amphotericin B lipid formulations are the major first-line treatment for mucormycosis (LFAB).[59,60] For infections of the central nervous system, the recommended dose of liposomal amphotericin B is 5 mg/kg/day, and it can go as high as 10 mg/kg/day. Patients in the French Mycosis Study Group's Ambiygyo study received 10 mg/kg/day of liposomal amphotericin B for the first month of treatment, along with surgery as needed. Between weeks 4 and 12, the overall response rate increased from 36% to 45%, 40% of patients had renal function impairment, which was evident by the serum creatinine level doubling (although 63% saw a brief increase).[61] Antifungal agent dosage recommendations continue to be a contentious topic. For triazoles like posaconazole and isavuconazole, this is valid. The ESCMID/ECMM guidelines suggest posaconazole be used as first-line treatment (moderate recommendation) at a dose of 200 mg of the oral suspension every six hours, in contrast to ECIL-6's advice that it be used as salvage treatment...
A recently formed triazole called isavuconazole has a broad spectrum of antifungal action, including Mucorales.[63] Isavuconazole 200 mg once daily (qd) (after six doses of 200 mg q8h) was given to 21 patients with mucormycosis as the primary treatment in a multicenter, open-label trial (VITAL trial). These patients were matched with contemporaneous controls from a registry of rare fungal diseases who had received conventional or lipid amphotericin B at a median dose of 70 or 325 250 mg qd, respectively.[64] Isavuconazole was therefore considered to be a substitute to amphotericin B as the first-line treatment for mucormycosis because the results in the two groups were comparable. Despite the positive findings, the study's limitations—namely, its small size and the matching of external controls—should be taken into consideration.[65]

The use of hyperbaric oxygen in an effort to create a more oxygen-enriched cell environment and the injection of cytokines concurrently with the antifungal medication are two other adjuvant therapies. Granulocyte-macrophage colony-stimulating factor and/or interferon-γ may boost the immune response against specific Mucorales, which may help treat the infection, according to in vitro and some preclinical findings.[66,67] however, these therapies should be utilized cautiously because there are no clinical studies on their use.

Iron chelators are an additional therapy option for mucormycosis. Deferasirox, an iron chelating drug, was discovered to boost survival rates in mice with mucormycosis and diabetic ketoacidosis in a murine model.[68] Deferasirox along with LFAB is also effective in rhino-orbital cerebral mucormycosis patients.[69]

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