

Mucormycosis: The black fungus

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The *Mucor* molds took full advantage when host defenses were down and the world was distracted by a pandemic. As clinicians were triaging massive severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) outbreaks, steroids were prescribed, likely compromising patients' immune systems and leaving them more susceptible to fungal invasion.

Aspergillus and *Candida* have been reported as the main fungal pathogens with COVID-19 but recently, during the delta variant, several cases of mucormycosis have been increasingly reported world-wide, particularly in India. Prolonged hospitalization, low oxygen levels, hyperglycemia, acidic medium, high iron levels and decreased phagocytic activity of white blood cells (WBC) due to immunosuppression along with several other shared risk factors apparently facilitated this opportunistic infection.¹⁻³

Mucormycosis is an angioinvasive, potentially fatal infection caused by *Zygomycetes* fungus members of the genus *Mucor* (Mucorales). It was previously known as Zygomycosis. The incidence is unknown but studies show a rising trend. Prevalence of mucormycosis in India is around 80 times as compared with the developed part of the world, approximately 0.14 cases per 1000 population.⁴ Data from the third world

countries show that diabetes mellitus is the main underlying disease, however in developed countries hematological malignancies and transplantation were the most common underlying diseases. Fungal spores enter the human body by inhalation, ingestion or direct inoculation.⁴

Fungal cell wall composition as well as genetic alterations help them in speedy growth inside the host environment and evade their defenses. There is a special iron assimilation mechanism inside fungal tissues while CotH proteins expressed on the spores and hyphae facilitate adhesion, angioinvasion, and dissemination. Lytic enzymes, mycotoxins and proteases augment fungal invasion.⁵

Mucormycosis is classified as pulmonary, cutaneous, gastrointestinal, rhinocerebral and disseminated forms, however endocarditis, osteomyelitis, peritonitis and renal mucormycosis are the rare varieties. The commonest predisposing factors of mucormycosis include diabetes mellitus, hematological malignancies, other malignancies, organ transplantation, prolonged neutropenia, use of corticosteroids, trauma, iron overload, illicit intravenous drug use, neonatal prematurity, low birthweight and malnourishment. Immunocompetent patients can also be affected, when the spores of the fungus are directly inoculated in the skin, as a result of trauma or burns.⁶

Healthcare-associated Mucormycosis has been attributed to various exposures in the hospital

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environment. The use of non-sterile products, bandages, adhesives, contaminated linens, wooden tongue depressors, ostomy bags and probiotics have all been implicated. Various procedures and devices, like catheters, insulin pumps and finger sticks, tooth extractions and surgeries have also contributed to this infection. Environmental factors may also be a source of infection. Molds may be found in the air, dust, water or any surfaces in the hospital. Construction works increase the risk of invasive fungal infections. Outbreaks have been linked to defective ventilation systems and water leakage.⁴

Its symptoms are usually related with the system involved. Most commonly fever, headache, facial pain, erythema and swelling of skin over eyes, nose or sinuses, scabs over the involved areas, nasal or sinus congestion are seen in Rhinocerebral mucormycosis. Pulmonary disease presents with fever, chest pain, shortness of breath, hemoptysis and productive cough, however, diffuse distension, vomiting, and gastrointestinal bleeds are the chief complaints of gastrointestinal variety of mucormycosis. Patients of disseminated variety are usually very sick and comatose.⁷

Diagnosis can be made on the basis of medical history, symptomatology, physical examinations, and laboratory tests. In clinical practice, laboratory investigations of mucormycosis includes histopathology, direct examination of wet mounts and culture. Since the disease is rare, a high index of suspicion is very important. Diagnosis consists of recognition of risk factors, assessment of clinical manifestations, early use of imaging modalities and prompt diagnosis and treatment based on histopathology, cultures and advanced molecular techniques.^{4,5} CT scan or MRI of the lungs, sinuses, or other parts of the body, depending on the location of the suspected infection might

help define the extent of infection or tissue destruction.

Liposomal amphotericin B (≥ 5 mg/kg) combined with surgical debridement is the first line treatment of Mucormycosis which also improves the outcome of the disease. Amphotericin B can be given intravenously, orally or topically but in few cases it has been administered in the form of aerosols, washes, soaked dressings, eye drops, intradiaphyseal cement beads, even thecal and in the form of percutaneous injections.

Isavuconazole and intravenous or delayed-release tablet forms of posaconazole are the second-line drugs.⁸

Amphotericin B loaded nanoemulsions were developed for topical use. It contains surfactants which can mechanically disrupt microbial membranes. Drug delivery systems such as nanoemulsions (NE) have proven ability to solubilize hydrophobic compounds, improve bioavailability and absorption, increase efficacy and reduce toxicity of encapsulated drugs. NE become even more attractive because they are inexpensive and easy to prepare.^{9,10}

New approaches to assess relationships between host, fungi, and antifungal drugs, and new routes of administration such as aerosols could improve mucormycosis treatment.

Prevention of COVID-associated mucormycosis can only be possible if we focus on the key factors. We should aim for better glycemic control in diabetics, unnecessary use of systemic corticosteroids, antibiotics, antifungal and other immunomodulatory drugs should be discouraged. Sterilized equipment and ventilation system of health facilities is a must. However early detection, proper wound care and

patient management can bring about the real difference.

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