# EDITORIAL

# Fatal Angioinvasive Mucormycosis 'Black Fungus', A Co-Infection in Covid-19 Patients, Requiring a Vigilant Eye Watch

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The pandemic of Corona viral infection disease-19 (COVID-19) had become a challenging task for the clinicians around the Globe. Despite the passage of near about one and a half year, yet many mysterious requires exploration to contain this fatal infection. The researchers and scientist are trying level best to identify ways for the reduction of morbidity and mortality rates from the said infection. But with the availability of vaccine things are heading towards betterment.

The COVID patients are found to be at risk of many serious complications. Presence of serious fungal infections is one of them. Few published studies are highlighting strong correlation amongst presence of superimposed angioinvasive *Mucormycocsis* (black fungus) in either acute illness or even in recovered patients. This rapidly progressing infection attacks the blood vessel and live tissues resulting in necrosis and blackening of area. Thus, giving it a name 'black fungus'. This superimposed infection requires somber attention, because it prolongs the recovery time of patients. The negligence can even lead to fatal outcomes.[1] The early case recognition and timely management for mucormycosis will be the only way out to reduce the miseries of COVID sufferers. *Mucormycosis or Zygomycosis* (older name), belongs to a category of opportunistic invasive fungal infection (IFIs). Either of the three commonly responsible fungi i.e *Rhizopus, Mucor, or Lichtheimia* belongs to the phylum *Zygomycota,* subphylum *Mucoromycotina*, order *Mucorales* and the family *Mucoraceae*. The members of this order are also well known as *Pin molds*. These are congregated as saprophytic molds in environment like soil , putrefying organic matter i.e dung piles, vegetable matter, leaves, rotten wood, etc.[2]

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Mucormycosis is a third communal, rare and fatal angioinvasive fungal infection i.e 2–6% of all IFIs. However, candidiasis and aspergillosis rank on first and second numbers. According to a published report for the year 2021, species wise frequency in patients with mucormycosis is 34% for Rhizopus species, 19% for both Mucor and Lichtheimia species. The reported mortality rate showed a range of 50% - 80% especially for the intraorbital or intracranial complications. However, country wise variation was observed as well. In India, *Rhizopus, Apophysomyces elegans, Anabaeana variabilis* and *Rhizopus homothallicus*, were identified to be the evolving responsible species. While less frequently identified species includes *Mucor irregularis* and *Thamnostylum lucknowense*. A Mexican study reported a new commonly responsible species of *Apophysomyces* i.e *Apophysomyces mexicanus*.[3] Other less frequently reported fungal infections includes oropharyngeal candidiasis, candidemia, pulmonary aspergillosis and pneumocystis jiroveci pneumonia.[4] Mucormycosis is usually a coinfection in conditions like pulmonary diseases, renal disorders, septic arthritis, dialysis-associated, peritonitis, gastritis, rhinocerebral and cranifacial mycormycosis. The involvement of mucous layer of skin, precisely cutaneous layer, predisposes to mucormycosis.[5]

In chronic state, the predisposing factors includes prolonged and severe neutropenia due to chemotherapeutic drugs, immunosuppression, hematologic malignancies, stem cell transplantation, and solid organ transplant recipients (SOTRs). Other factors can be previous respiratory pathology, uncontrolled diabetes mellitus (DM), iron overload, deferoxamine therapy, prolonged corticosteroid use, premature neonates, intravenous drug use, malnutrition, major trauma or burns, and impending nosocomial sources.[6]

The available data strongly supports that COVID

19 is a life-threatening illness. The pathogenesis involved over expression of inflammatory cytokines, and diminished cell-mediated immunity. A key factor for correlation amongst COVID-19 and mucormycosis is the decline in cluster of differentiation 4 and 8 positive T-helper (CD4+ T and CD8+ T) cell counts. While super added factors include hospital admissions in intensive care units (ICUs) requiring mechanical ventilation, prolonged hospital stays (>50 days), use of glucocorticoids and anti-viral drug remdesvir. [7] The situation further gets worsened with simultaneous use of immunomodulatory drugs like tocilizumab. All these promotes secondary infection in COVID patients. The common routes for acquiring mucormycosis is inhalation of fungal sporangiospores from environment or air. Direct inoculation into disrupted skin or mucosa of gastrointestinal tract can be the other source. Afterwards invasion to adjacent fat, muscle, fascia, and even bone. While secondary vascular invasion and hematogenous spread is common for cutaneous mucormycosis, which leads to high fatality rates.[2,3] The penetration of fungal hyphae to the orbits, brain, and meninges will cause infarction and necrosis of the involved tissues.[2,6] Therefore four recommended general principles harbors significance for managing mucormycosis i.e rapid diagnosis, elimination of predisposing factors, surgical debridement of infected tissue and appropriate antifungal therapy.

A European study reported the common clinical presentations of mucormycosis i.e rhino-orbital (34%), cerebral (34%), pulmonary (21%), cutaneous (20%), and disseminated mucormycosis (14%). The infection can rapidly progress to serious outcomes in <03 days' time. Therefore, a wise approach much be there for recognizing red flags of severity. These can be informed of neurological deficit, cranial nerve palsy, sinus pain, diplopia, periorbital swelling, proptosis, ulcers of the palate, complicated sinusitis with headache and fever. [1] Involvement of eyes or jawbone and osteomyelitis of the craniofacial skeleton, requires emergency surgical intervention to prevent the spread to brain. However, hyphal invasion of sinuses may follow a slow course of spread, even upto 04 weeks of time. The examination finding of nasal cavity or hard palate shows presence of black eschar due to necrosis of affected tissues.[3] As soon establishment of provisional diagnosis, confirmation can be done by taking samples from tissue debridement, tissue biopsy, nasal or upper respiratory tract by diagnostic nasal endoscopy.

In case of severity of illness, early diagnosis can be done on direct microscopy with potassium hydroxide (KOH) to identify the presence of hyphae.[5] Use of optical brighteners such as Blankophor and Calcofluor have proven effective for diagnosis on direct microscopy. While definitive diagnosis can be established by histological studies and fungal culture. The presence of broad aseptate, irregular, and ribbon-like, 6-15µm, broad hyphae, branching at right angles is the hall mark for confirmation. Hematoxylin and eosin (H&E), periodic acid-Schiff (PAS) or Grocott-Gomori's methenamine, and silver staining are commonly used satin to evaluate morphology on histopathology. Regarding the culture, Mucorales grow rapidly within 03 to 07 days of incubation on Sabouraud agar at 25°C to 30°C. While extent of infection can be identified with radiological support. The presence of multiple (≥10) nodules, reverse halo sign (RHS), and pleural effusion supports the diagnosis by computerized tomography (CT) scan.[2,3]

Enzyme-linked immunosorbent assays (ELISA), immunoblots, immunodiffusion tests, and Mucorales specific T cells by enzyme-linked immunospot (ELISpot) assay are the surrogate diagnostic markers. Molecular characterization can be studied by conventional polymerase chain reaction (PCR), restriction fragment length

polymorphism analyses (RFLP), and DNA sequencing. Most of the molecular assays targets internal transcribed spacer or the 18S rRNA genes.[3]

The recovery of COVID patients with mucormycosis is dependent upon early case recognition and prompt management. A combination of anti fungals and surgical debridement can improve treatment outcomes and patient's survival. Intra venous (I/V) amphotericin B is the recommended drug of choice for initial therapy for mucormycosis. Another study report concluded that synergistic effect achieved by a combination of I/V amphotericin B and caspofungin had proven more effective. Posaconazole oral suspension or Isavuconazonium (IV or oral) can be the other anti fungals for management. While intraorbital irrigation with amphotericin had been declared supportive for preventing the spread of craniofacial infection.[2] Mucormycosis belongs to a category of highly invasive and rapidly progressing severe fungal infection. The secondary origin of this coinfection with COVID-19 can lead to fatal outcome.[7] COVID-19 itself had taken more than one million lives around the Globe. Until the successful completion of phase three trials for many vaccines or specific antiviral therapy, supportive care plays a pivotal role in COVID management.[8]

As per recommended guidelines, timely tallying of broad-spectrum antibiotics, for COVID management offers upright cover for superimposed bacterial infection. While for fungal infections, due care is deficient. Adoption of a vigilant approach for early diagnosis and management is the only way out, to reduce high morbidity and mortality rate from this fatal co-infection. The Clinicians should be well aware for the possibility of its presence in COVID patients. While health policy makers from the Government should provide updated protocols for appropriate diagnostic and management option for this co existing mucormycosis. It will be the frontward step to combat this lethal infection.

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