

**MUCORMYCOSIS – AN EMERGING THREAT DURING COVID -19 OUTBREAK**

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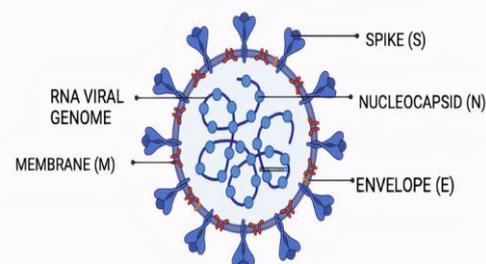
**ABSTRACT**

Recently in 2019, a global pandemic that originated from Wuhan, China, has imposed serious threat to population all over the globe. This COVID outbreak has taken lives of many and is still a major reason of worry. Though the symptoms of the disease are very similar to flu and includes cough, fever, sore throat and shortness of breath, but all these may infect the lungs severely, costing the lives of the patients. A more recent finding has shown that there are other opportunistic fungal and bacterial infections, affecting the COVID positive patients. One of them studied is about Mucormycosis, black fungus infection. The clinical symptoms of this fungal infection include blackening of skin, ulcers, blurring of vision, necrosis, and many more. This review presents the pathophysiology and clinical pathogenesis of Mucormycosis, implications and risk factors involved in the fungal infection, and its clinical diagnosis. This review also confers about the treatment and preventive measures involved for Mucormycosis.

**KEYWORDS:** COVID -19, Mucormycosis, diabetes mellitus, immunosuppressants, eye inflammation.**1. INTRODUCTION****1.1 COVID 19**

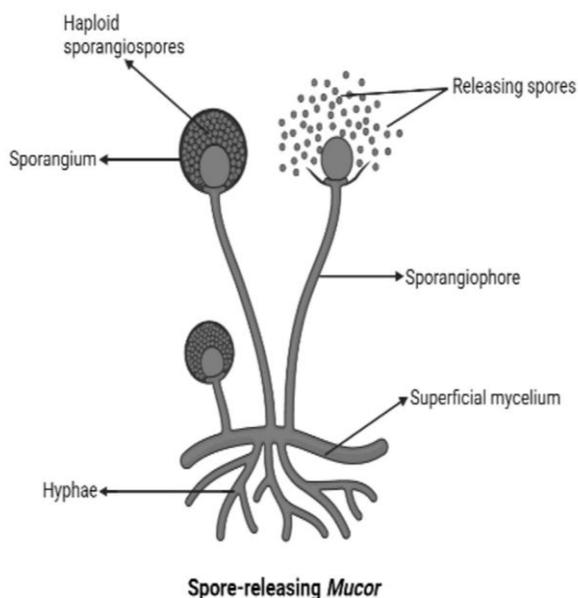
Severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2), a novel coronavirus, which causes severe pneumonia was discovered in Wuhan, China in December 2019 and since then it has been a threat to global health with a fatality rate of 2.3%.<sup>[1,2]</sup> It made its way to human host cell from the seafood market of Huanan, China.<sup>[3]</sup> The signs and symptoms vary according to the severity of the infection and particularly occur after 2 to 14 days of exposure, with some common ones being fever, cough, fatigue and/or shortness of breath.<sup>[4,5]</sup>

Coronaviruses are generally large single stranded positive RNAs enclosed in an envelope. They are spherical virions having a core shell and solar corona like surface projections (Latin: corona=crown).<sup>[3]</sup> Out of the four subfamilies namely alpha-, beta-, gamma-, and delta-; only alpha- and beta- are known to affect mammals.<sup>[1,3]</sup> It is detected by two types of laboratory studies: Molecular test; which mainly includes RT-PCR (Real time reverse transcriptase polymerase chain reaction) and Serological test; which includes ELISA and CDC (Enzyme linked immunosorbent assay and Human cell division cycle).<sup>[6,7]</sup> The presence of lymphopenia and high cytokine levels act as potential biomarkers for disease development, therefore improving these two and reducing inflammation can be used to treat COVID-19 patients.<sup>[8]</sup>

**Fig. 1: Structure of COVID.****1.2 BLACK FUNGUS and COVID -19**

Black fungus infection, also known as Mucormycosis, causing blackening effect on the skin, is seen to be a major reason of death nowadays, especially in COVID patients with a mortality rate being approximately 50%.<sup>[9-11]</sup> It belongs to the class zygomycetes and is caused by Rhizopus.<sup>[12,13]</sup> It is commonly seen in diabetic patients, as they have poorly controlled blood sugar, and affects the eye of these patients, often leading to a serious condition in which surgeons have to remove the eye.<sup>[10,14]</sup> This fungus takes the advantage of immunocompromised condition of the patients and hence is an opportunistic disease.<sup>[12]</sup> The clinical symptoms of the fungal infection include Pulmonary Mucormycosis, Disseminated Mucormycosis, Rhino Orbital Mucormycosis, and also affects some major organs of our body.<sup>[11,12,15]</sup>

Post COVID infection, some patients are observed to be infected by this deadly fungus whose plausible causes are found to be respiratory disorders, nosocomial infection, diabetes mellitus, significant immune suppression and systemic immune system alteration.<sup>[16,17]</sup> A further susceptibility to fungal infection is also by cytokine hyperproduction and breakdown of immunity mediated by cell.<sup>[16,18]</sup> Symptoms of black fungus infection noted in patients with stuffy and nosebleeds, eye inflammation, drooping eyelids, and if the condition worsen it may even lead to death of patients, especially those diagnosed with diabetes mellitus and a weak immune system.<sup>[19]</sup> Scientists are still conducting further studies to know all about Mucormycosis and why is it affecting COVID patients.<sup>[20]</sup>



**Fig. 2: Structure of Mucormycosis.**

## 2. Clinical Pathogenesis

Mucorales, the main causative agents that are responsible for Mucormycosis, penetrates into the respiratory tract by the route of inhalation of airborne spores, percutaneous inoculation or ingestion.<sup>[21-23]</sup> This fulminant invasive fungal infection majorly occurs in immunocompromised patients having conditions such as uncontrolled diabetes, renal failure, organ transplant, long-term corticosteroid, cirrhosis and AIDS.<sup>[24]</sup> When these spores reach lungs, they are encountered by mononuclear and polynuclear phagocytes, which kill the Mucorales by generation of oxidation metabolites and the cationic peptides defensins in a healthy host.<sup>[25]</sup> But due to phagocyte dysfunction in severely immunocompromised and neutropenic patients, there is a delayed movement of phagocytes at the site of action, making them more prone to develop the disease.<sup>[22,26]</sup> This leads to impaired chemotaxis and defective intracellular killing by both oxidative and non-oxidative mechanisms.<sup>[26]</sup> When these spores reach blood vessels, they cause hyphal invasion resulting in a combination of

haemorrhage, thrombosis, infarction and necrosis of tissue. But the proclivity of fungi for these vasculatures is still unknown.<sup>[21]</sup> The fungus can also spread to cerebral and orbital tissues, though it may take a long time to develop the infection.<sup>[27]</sup>

## 3. Implications and Risk Factors Involved

As reported by Kalal *et al*, patients infected with black fungus infection visit the hospital with a complaint of redness and pain near the eye and nose, which may also be associated with vomiting, fever and shortness of breath.<sup>[28]</sup> Since it is an opportunistic disease that occur due to administration of immunosuppressants, nowadays given to COVID patients, it has caused a major concern in the entire country because of its susceptibility to overpower the body's defence system.<sup>[29,30]</sup> This infection generally affects the eye, but is also seen to affect the central nervous system, gastrointestinal tract and respiratory tract.<sup>[28,29,31]</sup> Symptoms that occur as a result of the infection includes sinusitis, loosening of teeth, blackness over bridge of nose, blurred or double vision, thrombosis, necrosis and many more.<sup>[28]</sup> Although the infection is rare, but it is now seen among COVID patients in Intensive Care Units (ICU), with a history of diabetes mellitus, which is an accelerating cause of worsening of the fungal infection.<sup>[14,27]</sup> Other risk factors involved in the development of black fungus includes patients taking high doses of steroids, receiving anticancer treatment and patients on oxygen who required nasal prongs.<sup>[32,33]</sup>

Mucormycosis also affects the skin, leading to skin infections that include blisters and ulcers, turning the affected region black with redness and swelling in the infected wound.<sup>[27,34]</sup> Pulmonary Mucormycosis, a term related to the condition when black fungus affects the respiratory tract and harm the lungs, results in nose bleeds, nasal obstruction, loss of face feeling, cough, fever and chest discomfort.<sup>[34,35]</sup> It is extremely difficult to prevent Mucormycosis, as the fungus is ubiquitous in nature and enters the body by inhalation of spores, so it becomes important to treat the infection at an early stage, especially in COVID patients because of their weakened immune system.<sup>[18,36,37]</sup> If left untreated, it may lead to death of patients, so removing of eye is sometimes carried out by surgeons to save the life of patients.<sup>[38,39]</sup>

## 4. Diagnosis

### a) Clinical Presentation

As the primary site of inoculation of fungus is the nose and paranasal sinuses, the early signs are marked with facial numbness, pain or swelling in maxillary and facial region, dark coloured nasal discharge and/or nasal stuffiness.<sup>[40]</sup> Pleuritic pain in neutropenic host, which may signify an angioinvasive filamentous fungus and Diplopia in diabetic patients are some early manifestations of sino-orbital Mucormycosis.<sup>[41]</sup> A list of signs and symptoms proposed by Corzo-leon *et al* to diagnose rhino-cerebral Mucormycosis in diabetic patients that must be considered as 'red flags' includes

diplopia, sinus pain, proptosis, periorbital swelling, cranial nerve palsy, orbital apex syndrome, tissue necrosis and ulcers of palate.<sup>[42]</sup> Unfortunately, many people present after the disease has progressed into cranial vault which leads to blindness, lethargy, seizures and ultimately death.<sup>[40,42]</sup>

#### b) Radiological Features

Radiographic techniques include Positron emission tomography – computed tomography (PET/CT) of brain, orbital and paranasal sinuses with fluorodeoxyglucose that assists in the diagnosis and management of Mucormycosis.<sup>[42,43]</sup> Most common being the rhinosinusitis by radiological diagnosis, followed by orbital extension and intracranial invasion.<sup>[43]</sup> Pulmonary Mucormycosis is generally detected by CT scans in which characteristic reverse halo sign (RHS) is considered as an indicator the fungal infection.<sup>[42]</sup>

#### c) Microscopical and Histopathological Procedures

For rapid diagnosis of the fungal infection, we generally use direct microscopy (wet mount method) of the infected tissue with fluorescent brighteners, though

diagnosis through this method is not so accurate.<sup>[44]</sup> Different species of black fungus can be identified by microscopical examination after tissue biopsies.<sup>[45,46]</sup> Microbiological samples are generally taken from active lesions and grown on any carbohydrate substrate, where we can see the development of colonies within 24-48 hours, as they help in the definitive diagnosis of the infection.<sup>[43,47]</sup> Whereas histopathological diagnosis of Mucormycosis include biopsies of affected tissues and bronchopulmonary lavages.<sup>[47]</sup>

#### d) DNA Based Diagnosis

It is very difficult to detect the presence of pathogenic fungus in the human body, hence a DNA based detection of Mucormycosis is considered to be a reliable approach as it requires the identification of different regions of 18S and 28S rDNA and is considered a first line detection of Mucorales.<sup>[47,48]</sup> Nowadays a rapid molecular diagnosis of the infection is done by PCR assays.<sup>[45]</sup> Other molecular methods of detection of the fungi include nested PCR, qPCR, and restriction fragment length polymorphism analysis.<sup>[47]</sup>

S. No.	Diagnostic Method	Salient Features
1.	Clinical Presentation	It involves the identification of morphological changes such as blackening of skin, pain and swelling near eyes and nose, and visual loss. <sup>[42]</sup>
2.	Radiological Features	This includes detection by PET/CT scans. <sup>[15,16]</sup>
3.	Microscopy	Direct Microscopy and Fluorescent direct Microscopy. <sup>[20]</sup>
4.	Histopathology and Microbiology	These techniques include tissue biopsies and culturing of tissue in carbohydrate medium. <sup>[20]</sup>
5.	Molecular Techniques	DNA based diagnosis and PCR techniques are the common methods involved. <sup>[18,20]</sup>

#### 5. Treatment and Preventive Measures

- Treatment for Mucormycosis must be fast and aggressive due to the fact that by the time a presumptive diagnosis is made, the patient has suffered significant irreversible tissue damage.<sup>[49]</sup>
- We follow a multimodal therapeutic approach for Mucormycosis which include antifungals, surgical debridement and controlling the underlying condition which might predispose the patient to the disease.<sup>[50]</sup>
- The main drug used in antifungal therapy is amphotericin B (5-10mg/kg/day) which has significant in-vitro activity against zygomycetes and has been successfully used with its lipid formulations to treat Mucormycosis.<sup>[51,52]</sup>
- Controlling the blood sugar levels during covid-19 with or without steroids is an important preventive measure. If steroid use is required, it must be used judiciously with correct time, correct dose and correct duration.<sup>[28]</sup>
- Another alternative to amphotericin B as a first line treatment of Mucormycosis is Isavuconazole, which is a recently developed triazole which wide spectrum antifungal.<sup>[53]</sup>
- Salvage therapy options for patients with Mucormycosis who are intolerant to polyene therapy

includes Posaconazole or Deferasirox. Deferasirox should be used cautiously at a dose 20mg/kg/d for 2-4 weeks with regular monitoring of renal and hepatic functions.<sup>[54]</sup>

- Many immunosuppressants like tofacitinib, Baricitinib, bevacizumab and Itolizumab that are being used for severe covid-19 can be a possible risk factor and hence must be used judiciously with strict clinical monitoring.<sup>[55]</sup>
- A constant check should be kept on patients to detect risk factors like diabetes ketoacidosis (DKA), acidosis, hypoxia and leukopenia and necessary steps should be taken to keep them in control.<sup>[55]</sup>
- The humidifier bottle should be refilled, sterilised with normal saline and replaced at regular intervals for the patients using oxygen concentrator.<sup>[49]</sup>
- The use of immunomodulating drugs should be discontinued.<sup>[28]</sup>
- Surgical removal of the necrotic tissue along with the surrounding infected healthy-looking tissues must be done when needed and possible.<sup>[53,57]</sup>

#### CONCLUSION

A pandemic that emerged during 2019, still continues to be a major reason of death all over the globe. From this

review, we can conclude that COVID-19 has led to the evolution of many opportunistic fungal and bacterial infections, in which Mucormycosis is the most serious one. The black fungus infection is most recently observed in COVID patients, especially those who have a history of diabetes mellitus and are on life support. It is a major result of decreased immunity in the patients who are administered with immunosuppressants and steroids to treat the disease. It should also be noted that Mucormycosis is not an infection that can be avoided and left untreated, as it may worsen the condition of the patient and eventually taking his life. So, we can say that an immediate treatment is a need for the infected patients and should not be overlooked.

#### Abbreviations

COVID -19 – Coronavirus Disease of 2019

SARS-CoV-2 – Severe Acute Respiratory Syndrome Coronavirus-2

ELISA – Enzyme linked immunosorbent assay

CDC – Cell division cycle

ICU – Intensive care units

PET/CT – Positron emission tomography – computed tomography

PCR – Polymerase chain reaction

DNA – Deoxyribonucleic acid

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