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Mucormycosis or Black Fungus: An Emerging Threat among Covid-19 Patients in India

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Abstract: ***Following the first wave of Covid-19, the second wave wreaks havoc on Indians, infecting them with a mysterious fungal condition known as Mucormycosis (Black fungus). The researchers discovered that using immunosuppressive drugs to treat Covid-19 increased the likelihood of contracting mucormycosis. Mucormycosis molds are more likely to affect patients with (have or who went through) hyperglycemia, ketoacidosis, solid organ or bone marrow transplantation, liver cirrhosis, and neutropenia. To eradicate Mucormycosis, four primary variables must be addressed: early diagnosis, removal of predisposing factors, timely antifungal therapy, surgical removal of all infected tissues, and adjuvant therapies. The management of the diseases is dependent on accurate diagnosis and prompt treatment, which may include antifungal agents as well as surgical intervention with the involved tissues. Many new agents with antimicrobial activity against Mucorales are being studied in addition to the traditional and well-proven first-line therapy of amphotericin B-based drugs or posaconazole.***
Keywords: Black Fungus, Mucormycosis, Amphotericin B, Posaconazole

I. INTRODUCTION

The worldwide pandemic Covid-19, caused by "Severe acute respiratory syndrome Coronavirus-2 (SARS-CoV-2)," has had a significant impact on India and even worldwide (Ramteke, Sahu, 2019). The first case of COVID-19 was recorded in Kerala, India on January 30, 2020, and by May 2020, most cases, i.e., 1 lakh per day, had been reported for the year (Andrews *et al*, 2020). After mid-June, patient recovery increased in lockstep with a decline in infection incidence, and active cases fell below 15000 in Jan 2021. After that, in March 2021, the second wave began, with a much greater number of active cases than the first wave, due to a lack of hospital beds, vaccines, medicines, oxygen cylinders, and oxygen. At the beginning of May 2021, the daily reported cases had risen to around 4.5 lakhs. Covid-19 has a broad variety of effects, from mild to severe to even life-threatening, and is linked to several ailments, including diabetes, heart disease, and immune system issues. (Gandhi *et al*, 2020; Apicella *et al*, 2020). Also, few of the articles also reported the development of diseases like pneumonia, candidiasis, pulmonary aspergillosis, etc in Covid-19 patients. (Salehi *et al*, 2020; Chowdhary *et al*, 2020). There have also been accounts of Covid-19 patients developing a mystery fungal condition known as Mucormycosis or Black Fungus**.** (Sarkar *et al*, 2021)**.** Covid-19 patients in India have also been severely affected by this pandemic disease (black fungus), with a total of 8848 cases recorded as of May 22, 2021. (Afroze *et al*, 2017)

II. MUCORMYCOSIS OR BLACK FUNGUS

Mucormycosis is also known as a black fungus. The term came to light because it causes necrosis in the affected tissue of the patient's skin, turning it black in color.After candidiasis and aspergillosis, "mucormycosis" is the least common kind of fungal infection. *Mucormycetes*, which belong to the class Zygomycetes and the order *Mucorales*, are the cause. This mold can be found in soil, leaves, rotting wood, manure, and other places. Species of Mucoraceae are *Rhizopus arrhizus, Rhizopus pusillus, Apophysomyces elegans, Absidia elegans, and Mucor racemosus*. (Prabhu *et al*, 2004; Ribes *et al*, 2000; Mohindra *et al*, 2007)

III. CLINICAL PATHOGENESIS

Mucormycetes mold has the ability to enter vulnerable hosts through the nostrils, mouth, or burned/ruptured skin, causing infections in the rhino-orbito-cerebral, gastrointestinal, or cutaneous wounds (Mohindra *et al*, 2007). It can also lead to tissue necrosis and result in vascular thrombosis (Rapidis, 2009). According to research, it was found that rhino cerebral Mucormycosis is the most common type of Mucormycosis. Patients with uncontrolled diabetes and leukemia are the most likely to develop it. When rhino-cerebral Mucormycosis progresses, it can spread to the central nervous system and be fatal. Lungs and sinuses may be the second most common infection location. The mortality rate associated with lung infection could be as high as 60%. (Spellberg *et al*, 2005)
In such extreme covid 19 conditions the patient's immune system developed dysfunctional, with a reduction in lymphocyte numbers and an exponential surge in inflammatory cytokines like IL-6, IL-1β, IFN- γ, MCP-1, IP-10, IL-4, IL-10 and Tumor necrosis factor

(TNF) which lead to inflammation in the lungs and could even lead to death. (Zhou *et al,* 2020; Song *et al,* 2020) Because of the seriousness of hyper inflammation doctors prefer the utilization of immunosuppressants or steroids as a life-saving treatment in critically severe patients. A steroid decrease swelling in the lungs and even it reduces the immunity of the body and increases the glucose levels in both diabetic and typical patients. (Zhou *et al,* 2020) According to the doctor, immunosuppressed patients are bound to be impacted by Mucormycosis growth. (Shang *et al,* 2020; Pak *et al,* 2008)

SARS coronavirus 2 enters the body through a spike protein on the envelope that attaches to angiotensin-converting enzyme 2 (ACE 2), which is found in pancreatic beta cells, the lungs, and the kidney, and the small intestine. It's probable that virus infection of pancreatic cells damages beta cells, resulting in insulin insufficiency. (Bourgonje *et al,* 2020; Zou *et al,* 2020) Mucormycosis molds are more likely to assault patients with hyperglycemia and ketoacidosis. (Maertens *et al,* 1999; Kontoyiannis *et al,* 2000). Treatment of Covid-19 patients with immunosuppressants who have uncontrolled diabetes and ketoacidosis puts them at risk for Mucormycosis because it creates malfunctioning phagocytes, which results in decreased intracellular killing by both oxidative and non-oxidative mechanisms. (Ahmadikia *et al,* 2021)

The pathogenesis of diabetes mellitus patients in ketoacidosis further revealed that hyperglycemia and an acidic pH (7.3–6.88) lead to an increase in free iron in the blood, which is caused by iron being released from binding proteins. Mucormycosis molds like *Rhizopus arrhizu* and *Rhizopus oryzae* thrive on this free iron. (Ibrahim *et al,* 2012)

Also, because deferoxamine is an iron chelator, patients receiving it are more likely to be attacked by Rhizopus species. According to studies, fungus siderophores have a stronger affinity for iron than deferoxamine, allowing them to easily extract iron from deferoxamine and supply it to the fungus. (Locht *et al,* 1994; Boelaert *et al,* 1993). Fat adipose tissue also generates adipokines, which influence glucose metabolism by releasing excessive amounts of inflammatory cytokines (IL-6, IL-8, TNF-) and causing hyperinflammation. (Ouchi *et al.,* 2009; Eder *et al.,* 2009). Adipose tissues in an obese patient also promote the mitochondrial synthesis of oxygen-reactive species (ROS). (Manna *et al,* 2015). Higher levels of ROS in a hyperglycemic condition promote increased glycosylation and protein kinase C activation. As a result, obese Covid-19 patients are more likely to be infected with Mucormycosis. (Brownlee, 2005). Mucormycosis infection is more likely in patients who have had a bone marrow transplant, liver cirrhosis, or neutropenia. Because these patients have fewer monocytes and neutrophils count and are less able to fight the mucormycetes mold. (Pak *et al*., 2008; Prakash, Chakrabarti, 2019; Novak *et al,* 2017)

As a result, the inference is that a Covid patient with a lower number of monocytes and neutrophils is more likely to contract mucormycosis. As stated previously, people with diabetes mellitus, ketoacidosis, impaired immunity, and patients on immunosuppressants/ corticosteroids, as in the case of Covid-19, have an increased risk of developing Mucormycosis mold. The most common source of Mucormycosis mold development or inoculation is the pollution of water and soil (Novak *et al,* 2017)**.**In the instance of Covid-19, the source could be water for the humidifier during oxygen therapy before the patients inhale inside. The infection is potentially fatal, with a mortality rate of 38–80 percent.

IV. SIGNS AND SYMPTOMS

Fever, headache, and reddish swollen skin over the nose and around the eyes are all major signs and symptoms of Mucormycosis during or after therapy with Covid-19. (AK, Gupta, 2021). Patients also reported visual abnormalities, eye swelling, ocular pain, facial edema, and breath shortening. Diabetic individuals have also reported symptoms of diplopia, which is an infection indicator. (Spellberg *et al,* 2005)**.** Sinus pain, proptosis, periorbital inflammation, orbital apex syndrome, ulcer of the palate, and cranial nerve palsy are the main symptoms of Mucormycosis infection, according to scientific terminology. (Mukherjee *et al,* 2016)

V. DIAGNOSIS

Mucormycosis is quite difficult to diagnose, and a challenging task for physicians, based on the identification of specific symptoms, a complete patient history, a thorough clinical evaluation, and specialist tests. Mucormycosis does not respond to any antigen detection tests, however, aspergillosis can be detected with a galactomannan antigen test. (Ribes *et al,* 2000)**.** Mucorales produce non-pigmented, broad (5–20 m), thin-walled, ribbon-like hyphae, which can be distinguished from Aspergillus or other hyaline molds using histopathology of infected tissue**.** (Ribes *et al,* 2000). The culture of specimens can develop rapidly at temperatures of 24–37°C in a time range of 24–48 hours, making specimen culture a significant approach. The tissue culture approach enables genus and species-level identification. (Walsh *et al,* 2012)

Early identification (Milon L *et al,* 2016) and monitoring of mucormycosis by quantitative polymerase chain reaction detection of circulating DNA in serum, which is difficult to diagnose by histopathological examination.

The approach described has strong specificity and no cross-amplification with other prevalent fungal infection-causing species such as Fusarium, Aspergillus, or Scedosporium. Furthermore, patients who are unable to undergo a biopsy or who have severe thrombocytopenia due to hematologic malignancies can benefit from the qPCR approach. (Millon *et al,* 2016).

VI. TREATMENT

In order to eradicate Mucormycosis, four primary variables were addressed: early diagnosis, removal of predisposing factors, timely antifungal therapy, surgical removal of all infected tissues, and adjuvant therapies. (Nithyanandam *et al.,* 2003). Only in cases of rhino-cerebral and cutaneous infection can imaging investigations and nasal endoscopy be used to make a diagnosis. (Khor *et al.,* 2010; Million *et al,*2013) showed a polymerase chain reaction (PCR) method which detects Mucorales DNA in blood samples three days before Mucormycosis diagnosis (Millon *et al,* 2013)**.** If a Covid 19 patient with diabetes, complains of headaches and vision problems, he or she should be checked for Mucormycosis using imaging techniques and a nasal endoscopy. Early discovery in such a scenario could save a person's life because the fungus can infiltrate the cranium and cause death later on. For the proper treatment of Mucormycosis infection, all predisposing variables must be removed and regulated. Controlling hyperglycemia while reversing ketoacidosis may lead to the reversal of Mucorales invading host tissues, as diabetes with ketoacidosis is a concerning issue among Indian patients. (Spellberg *et al,* 2005). In this regard, a study found that combining sodium bicarbonate with insulin could help diabetic ketoacidosis be reversed (Gebremariam *et al,* 2016). Immunosuppressive medications, primarily steroids, and deferoxamine, are used in moderation or not at all to prevent Mucorales from invading host tissues. (Ribes *et al,* 2000)

The best treatment for mucormycosis is to remove affected tissues if at all possible. However, while this is easy in some circumstances, such as rhino-cerebral or cutaneous infection, it is impossible in many others, such as pulmonary sickness or when the virus has infected the brain. (Millon *et al,* 2013) Early surgical excision of infected sinuses in rhino-cerebral mucormycosis prevents infection from spreading to the eyes, according to a study, leading to 85 percent cure rates. In a study, it was also discovered that using antifungal drugs during surgery lowered mortality from 70% to 14%. (Nithyanandam *et al,* 2003)

In a few studies, it was found that the application of Amphotericin B is preferred as an antifungal drug for the treatment of mucormycosis infection. Liposomal amphotericin B with a low dose of 5 mg/g/day to a higher dose of 10 mg/kg/day for cerebral infection patients is most preferred as of low toxicity and higher CNS penetration (Barron *et al,* 2005; Cagatay *et al,* 2001). However, the length of the time of Amphotericin B treatment is still not fully documented, even though it was used. a physician's decision based on the patient's underlying condition. According to some reports, treatment should last at least three weeks. If radiological and clinical improvement is seen, triazoles such as posaconazole, isavuconazole, voriconazole, and others are added to the treatment. (Kontoyiannis *et al,* 2011; Cornely *et al,* 2019)

In an experiment with a murine model, low doses of Caspofungin alone demonstrated minimal effectiveness against Mucorales in vitro, but it had a synergistic impact when combined with amphotericin B. It is quite low in toxicity. Caspofungin was discovered to be efficient in an in-vitro activity by inhibiting (1–3)-β-D-glucan synthetase enzyme expressed by *Rhizopus oryzae* (Spellberg *et al,* 2005; Ibrahim *et al,* 2005). Other chelators, including deferoxamine, are used as a supplementary therapy. Iron chelators prevented the fungus from absorbing iron and hence preventing its growth, whereas deferoxamine promoted mold growth. (Boelaert *et al,* 1994). The use of hyperbaric oxygen also inhibits the growth of Mucormycosis mold, as increased oxygen pressure boosts neutrophils' capacity to kill the molds. (Ferguson *et al,* 1988)

VII. CONCLUSION

In the current scenario of Covid 19, Immunosuppressive therapy has been a key strategy in reducing the severity of hyper inflammation or viral load in Covid-19 patients, but it also raises the risk of infection with mucormycosis. Patients with uncontrolled diabetes, leukemia, or ketoacidosis are at a higher risk of becoming infected with mucormycosis. Patients with solid organ or bone marrow transplantation, liver cirrhosis, and neutropenia are more likely to become infected with mucormycosis, so healthcare practitioners must consider their patient's past history when treating Covid-19. Patients should report any sort of Mucormycosis sign or symptom, such as fever, headache, or reddish swollen skin over the nose and around the eyes, as soon as possible since early identification and removal of infected parts with antifungal therapy is the most effective way to eradicate the illness. For effective prevention, more research is required and in Covid-19, suppression of opportunistic mucormycosis infection patients. In addition, the use of immunosuppressants with Covid-19 treatment requires additional refining.

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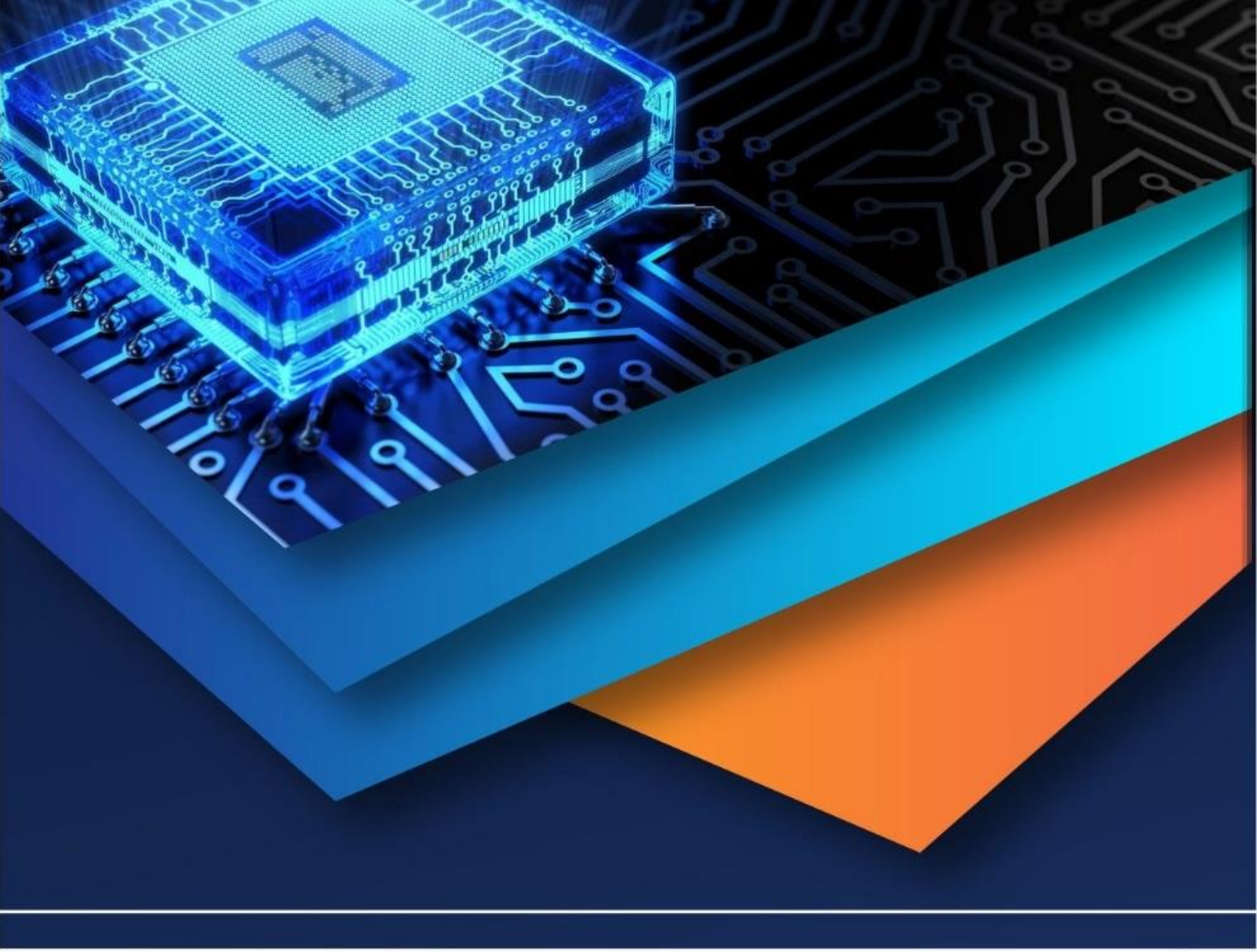

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