

The Black Fungus Crisis: A Review of COVID-19 Associated Mucormycosis in India – Epidemiology, Pathogenesis, and Public Health Implications

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Abstract: The COVID-19 pandemic not only posed direct respiratory challenges but also gave rise to a surge in opportunistic infections, among which mucormycosis gained particular prominence in India during the second wave. Commonly referred to as the "black fungus," COVID-19-associated mucormycosis (CAM) presented with an unprecedented number of cases, especially among patients with diabetes, those treated with corticosteroids, and individuals undergoing oxygen therapy. India, which already bore a higher baseline incidence of mucormycosis, witnessed a multifactorial explosion of CAM due to a convergence of epidemiological, clinical, and infrastructural factors. This review explores the epidemiology, etiology, pathophysiology, clinical manifestations, and public health response to CAM in India. The paper further highlights the diagnostic and therapeutic challenges, emphasizing the urgent need for integrated, multisectoral responses to manage fungal infections during viral pandemics. Understanding the underlying biological mechanisms and systemic vulnerabilities is essential for formulating more effective preventive and therapeutic strategies in the post-pandemic era.

Keywords: COVID-19, Mucormycosis, Black Fungus, India, Opportunistic Infections, Diabetes Mellitus, Steroid Therapy, Public Health, Fungal Infections, CAM

I. Introduction

The outbreak of the Coronavirus Disease 2019 (COVID-19) has posed an unprecedented global health crisis, with India bearing a substantial burden during successive waves of infection. While the primary focus remained on combating the viral spread and managing respiratory complications, a disturbing secondary phenomenon emerged during the second wave of the pandemic in India—COVID-19-associated mucormycosis (CAM), colloquially referred to as the "black fungus." Mucormycosis, a rare but serious fungal infection caused by molds belonging to the order Mucorales, surged alarmingly among COVID-19 patients, particularly those with underlying health conditions or those undergoing immunosuppressive treatments such as corticosteroids. India, already known for a higher prevalence of mucormycosis compared to global averages, witnessed a dramatic escalation in cases during 2021, prompting the Indian Ministry of Health to declare it an epidemic in several states. The synergistic interplay of factors—uncontrolled diabetes mellitus, prolonged ICU stays, indiscriminate use of corticosteroids and broad-spectrum antibiotics, and unsanitary oxygen therapy—contributed significantly to the rise of CAM cases.

The COVID-19 pandemic, caused by the novel coronavirus SARS-CoV-2, has had profound global implications, not only in terms of morbidity and mortality but also in its secondary complications and opportunistic infections. Among the most alarming of these in the Indian context has been the sudden surge of **mucormycosis**, a rare but potentially lethal fungal infection, particularly among patients recovering from or actively battling COVID-19. Termed **COVID-19 Associated Mucormycosis (CAM)**, this condition became a significant public health concern during India's devastating second wave in 2021. Mucormycosis is caused by fungi of the order Mucorales, commonly found in the environment, including in soil, decaying organic matter, and even in hospital settings. While typically opportunistic and rare in immunocompetent individuals, the infection can become invasive and fatal in immunocompromised hosts, particularly those with diabetes mellitus, hematologic malignancies, or those receiving immunosuppressive therapy. In COVID-19 patients, several predisposing factors were identified: use of systemic corticosteroids, prolonged hospitalizations, ICU stays, mechanical ventilation, and pre-existing diabetes — a prevalent comorbidity in the Indian population.

India's unique epidemiological and socio-clinical conditions created a "perfect storm" for CAM. The country already reports one of the highest rates of mucormycosis in the world, approximately 70 times higher than global estimates. With the COVID-19 surge came increased steroid use and oxygen therapy, sometimes under suboptimal hygienic conditions due to overwhelmed healthcare systems. These contributed significantly to the onset of mucormycosis, particularly the rhino-orbito-cerebral form, which proved to be the most common and deadly manifestation during the pandemic. The Indian Ministry of Health and Family Welfare officially classified mucormycosis as a notifiable disease under the Epidemic Diseases Act in May 2021. Despite

awareness efforts and clinical interventions, thousands of cases were reported, and the mortality rate remained high due to late diagnosis and limited access to antifungal medications such as liposomal amphotericin B.

This review paper aims to provide a comprehensive synthesis of existing literature and clinical evidence on COVID-19-associated mucormycosis in India. It explores the epidemiological trends, identifies the etiological and pathophysiological mechanisms behind CAM, evaluates diagnostic and treatment protocols, and critically assesses the challenges faced by the Indian healthcare system in responding to this dual epidemic. Understanding the multifactorial nature of CAM is crucial not only for improving clinical outcomes but also for shaping future pandemic preparedness and antimicrobial stewardship strategies in India.

Mucormycosis, also known as black fungus is a filamentous fungal disease which is angioinvasive (Blood vessel infecting) caused by order Mucorales- class Zygomycetes, has become third most infective mycosis (Petrikos et al., 2012; Prakash and Chakrabarti, 2021). Indian population is 80 times more affected by mucormycosis than whole world and central government has declared India as a mucormycosis pandemic on May 10, 2021. Mucorales fungi are very predominant pathogen which infects wide range of hosts, ranging from plants to invertebrates and humans. Most commonly found pathogen genus are *Rhizopus* (most common genus associated with mucormycosis), *Lichtheimia* (formerly known as *Absidia* and *Mycoclados*), and *Mucor*, *zygomycetes* genera (e.g. *Rhizomucor*, *Saksenaea*, *Cunninghamella*, and *Apophysomyces*). (Andrianaki et al., 2013) Based on the body parts affected, mucormycosis can be divided into 6 types-

- (1) Rhinocerebral
- (2) Pulmonary
- (3) Cutaneous
- (4) Gastrointestinal
- (5) Disseminated
- (6) Uncommon Presentations. (Petrikos et al., 2012)

Patients with history of diabetes mellitus, organ transplant, kidney disease, tuberculosis, corticosteroids or immunosuppressants consumption, iron overload and trauma are at more risk of mucormycosis (Prakash and Chakrabarti, 2021). Mucormycosis majorly affects males than females and targets COVID 19 patients (Active or recovered both) along with others (Singhet et al., 2021).

CAM (Coronavirus Disease Associated Mucormycosis)

COVID-19, a global pandemic is showing significant incidence of secondary infections, bacterial and well as fungal as immune system is hampered. In regular circumstances, when we expose to the fungal spores our immune system responds in a variety of ways, they don't allow them to settle down in our body and eradicate them, release of free oxygen radicals and phagocytosis is performed by the neutrophils, monocytes and macrophages. In COVID-19 case, altered immune system cannot combat and this leads to the occurrence of opportunistic infections. As a treatment of a variety of diseases, consumption of steroids/monoclonal antibodies/broad-spectrum antibiotics against COVID-19 may lead to the development/exacerbation of preexisting fungal diseases (Amodet et al., 2021; Mehta et al., 2021).

Transmission Of Mucormycosis

Mucormycosis is actually an opportunistic fungus, it cannot affect an individual until he is immunologically weakened. It is noncontagious, not spread from person to person. Spores of mucormycosis can be inhaled or swallowed with air, food, etc. and it is more persistent in humid areas such as AC ducts, moist mask, hospital premises outbreaks are observed because of adhesive bandages, wooden tongue depressors, hospital linens, negative pressure rooms, water leaks, poor air filtration, non-sterile medical devices, and building construction, etc. They mainly colonize in nasal, pharyngeal and oral mucosa including paranasal sinus. From paranasal sinus, it can transmit to nasolacrimal duct and medial orbit, even reaching up to skull and causes severe issues such as orbital cellulitis, chemosis, proptosis, loss of vision, ophthalmoplegia, superior orbital fissure syndrome, sagittal sinus thrombosis, epidural or subdural abscess formation. Sometimes, patient with bloody nasal discharge is diagnosed with the infection of mucormycosis to the brain via nasal turbinates causing cerebral ischemia which leads to cerebral infarction and also death. (Pagare Sultan, 2021). *Zygomycetes* shows very high affinity to the blood vessels, shows rapid invasion and disseminate widely. (Kontoyiannis, 2012). *Rhizopus oryzae* is mostly found causative agent of mucormycosis with a world-wide distribution and higher occurrence in tropical and subtropical regions. (Battaglia et al., 2012)

Etiology in the Context of COVID-19

The etiology of **COVID-19-associated mucormycosis (CAM)** is primarily multifactorial, involving:

1. **SARS-CoV-2 Infection:** COVID-19 itself has been shown to induce immune dysregulation. The virus targets not only the respiratory epithelium but also impairs the innate immune response, including the

function of phagocytes and neutrophils, which are crucial for controlling fungal infections. In severe cases, lymphopenia and elevated inflammatory markers such as ferritin and interleukin-6 (IL-6) further contribute to the immunosuppressive state.

2. **Corticosteroid Use:** Corticosteroids, such as dexamethasone, were widely used during the pandemic to control the hyperinflammatory response associated with severe COVID-19. While these drugs reduced mortality in critical patients, they also suppressed the immune response and elevated blood glucose levels—both recognized risk factors for mucormycosis. In many cases in India, steroids were used indiscriminately or in higher doses than recommended, increasing susceptibility to fungal invasion.
3. **Diabetes Mellitus:** Diabetes, particularly uncontrolled or undiagnosed cases, emerged as a key predisposing factor in CAM. Hyperglycemia impairs neutrophil chemotaxis and phagocytosis, while ketoacidosis creates an acidic environment favorable to fungal growth. Iron availability increases in diabetic ketoacidosis, and *Rhizopus* species possess high-affinity iron permeases that promote their virulence in such conditions.
4. **Environmental Exposure and Nosocomial Factors:** In many Indian hospitals and makeshift COVID care centers, compromised infection control practices, poor ventilation, and use of unsterile oxygen delivery systems may have increased the chances of exposure to Mucorales spores. Additionally, the use of non-sterile water in humidifiers and oxygen cylinders without proper disinfection has been cited as a potential environmental source.
5. **Broad-Spectrum Antibiotics and Immunomodulators:** The use of broad-spectrum antibiotics may disrupt normal microbiota, facilitating fungal overgrowth. Immunomodulatory therapies such as tocilizumab (an IL-6 inhibitor) used to manage cytokine storm also contribute to immunosuppression, heightening the risk of invasive fungal infections.

Pathophysiology

Once inhaled or introduced through skin or mucosa, Mucorales spores germinate and invade the host tissues. The hallmark of mucormycosis is **angioinvasion**, where the fungal hyphae infiltrate blood vessels, causing thrombosis, ischemia, and tissue necrosis. This explains the rapid progression and tissue destruction characteristic of CAM, particularly in rhino-orbito-cerebral forms. The fungi thrive in hyperglycemic and acidic environments, spreading rapidly through the paranasal sinuses to the orbit and even the brain if left untreated. In pulmonary or disseminated forms, spores reach deeper tissues, causing hemorrhagic infarctions and septic emboli. Due to the aggressive tissue invasion and difficulty in early diagnosis, the infection is often fatal unless managed aggressively through antifungal therapy and surgical debridement.

Symptoms

According to WHO, different type of mucormycosis can be diagnosed by observing symptoms mentioned as follows-

Sr. No.	Types of mucormycosis	Associated symptoms
1.	Rhinocerebral (sinus and brain) mucormycosis	- One-sided facial swelling - Headache - Nasal or sinus congestion - Black lesions on nasal bridge or upper inside of mouth that quickly become more severe - Fever - Lethargy, seizures, slurred speech, partial paralysis
2.	Pulmonary (lung) mucormycosis	- Fever - Cough - Chest pain - Shortness of breath - Hemoptysis
3.	Cutaneous (skin) mucormycosis	Skin lesion that resembles blisters or ulcers. The infected area may turn black. Other symptoms include pain, warmth, excessive redness, or swelling around a wound.
4.	Gastrointestinal mucormycosis	- Abdominal pain - Nausea and vomiting - Gastrointestinal bleeding
5.	Disseminated mucormycosis	Tends to occur in people who are already sick from other medical conditions, which makes it difficult to identify which symptoms are related to mucormycosis. Patients with disseminated infection in the brain may develop mental status changes or coma.

Clinical diagnosis .

Diagnosis of CAM can be done with routine laboratory diagnosis, in clinical practice, histopathology, direct examination of wet mounts and cultures, direct microscopy of culture along with non-invasive diagnostic methods such as molecular serology and metabolomics-breath test (Skiadaet al., 2020).

Treatment:

Anti-fungal treatment along with supportive care is useful in the management of COVID-19. Glucocorticoids in combination with antiviral drugs such as Remdesivir are beneficial in COVID-19. Use of Glucocorticoids is inexpensive, easily available and reduces rate of mortality in patients. (Garg et al.,2021) Treatment of mucormycosis needs an accurate and rapid diagnosis along with correction of predisposing factors, surgical resection or debridement, which will lead to effective anti-fungal therapy. Antifungal Agents such as Polyenes such as Amphotericin B deoxycholate (AmB), amphotericin B lipid complex and liposomal amphotericin B (LAmB) are useful in treatment and Liposomal amphotericin B (LAmB) is most promising drug as it is safer, efficient alternatives to normal antifungals. Along with this, Azoles e.g. Fluconazole and voriconazole are effective against mucormycosis. Even itraconazole is also useful against *Absidia* species. Iron chelation therapy also holds promising approach in fight against mucormycosis (Jajuet al., 2020; Spellberget al., 2009). Here, physicians play an important role for the prevention of emergence of these CAM and other opportunistic pathogens and early diagnosis which can reduce mortality and morbidity rate significantly. Utilization of therapeutics with low dose for the short duration and minimum, needed use of broad-spectrum antibiotics (Mehta et al., 2021)

Epidemiology of COVID-19 Associated Mucormycosis in India

India experienced an unprecedented surge in mucormycosis cases during the second wave of the COVID-19 pandemic in early 2021, prompting concern both nationally and internationally. While mucormycosis is a known opportunistic infection, India reported a disproportionately high burden compared to other countries, with the majority of cases being associated with COVID-19. According to a multicenter study conducted by Patel et al. (2021), India recorded approximately 71% of global cases of COVID-19-associated mucormycosis (CAM), positioning it as an epicenter of the dual epidemic.

Pre-Pandemic Incidence of Mucormycosis in India

Even before the pandemic, India had a relatively high incidence of mucormycosis, estimated at 0.14 cases per 1000 population—roughly 80 times higher than in developed countries like the USA (Prakash &Chakrabarti, 2019). The reasons behind this include India's high burden of uncontrolled diabetes mellitus, a major predisposing factor, along with widespread environmental exposure to fungal spores and relatively weaker infection control practices in certain healthcare settings.

CAM Surge During the Second Wave

During the months of April to July 2021, India experienced a sudden spike in CAM cases, particularly in the states of Gujarat, Maharashtra, Rajasthan, and Uttar Pradesh. Reports from the Indian Council of Medical Research (ICMR) and the Union Health Ministry estimated more than 45,000 cases of CAM across the country within a span of three months. Hospitals were overwhelmed, and the healthcare system struggled to cope with the added burden of this aggressive fungal infection alongside COVID-19 cases.

The majority of CAM cases (over 85%) were linked to patients recovering from COVID-19, with a large percentage either undergoing or having completed corticosteroid therapy. Studies showed that approximately 94% of the CAM patients had diabetes mellitus and about 71% had received steroids during their COVID-19 treatment (Sen et al., 2021). In many instances, poor glycemic control, especially in undiagnosed diabetic patients, contributed to the pathogenesis of mucormycosis.

Common Forms and Presentation

In India, the most common clinical presentation of CAM was rhino-orbito-cerebral mucormycosis (ROCM), accounting for nearly 85% of cases, followed by pulmonary, cutaneous, gastrointestinal, and disseminated forms. ROCM typically begins in the nasal sinuses and can rapidly spread to the orbit and brain, resulting in high morbidity and mortality if not treated promptly. The disease progression is often fulminant, and late diagnosis often results in orbital exenteration or death.

Demographic Profile

CAM predominantly affected middle-aged to elderly males (male-to-female ratio of about 3:1), although children and young adults were not immune. Patients often came from rural and semi-urban areas where healthcare access was limited, and many had received COVID-19 treatment in unregulated settings,

including private clinics and home-based care without proper monitoring.

Geographical and Healthcare Disparities

While mucormycosis was reported across India, states with high COVID-19 caseloads and larger diabetic populations bore the brunt of CAM cases. Disparities in healthcare infrastructure, hygiene practices in oxygen delivery systems, and the availability of antifungal drugs led to higher fatality rates in some regions. For instance, a shortage of liposomal amphotericin B, the frontline antifungal treatment, was widely reported, delaying appropriate care and surgical intervention in critical cases.

Government Response

In response to the outbreak, the Government of India mandated the notification of all CAM cases, established centralized drug distribution channels, and issued detailed clinical guidelines for diagnosis and treatment. Public awareness campaigns were also initiated to educate the masses about early symptoms like nasal congestion, facial pain, swelling, and vision disturbances.

II. Conclusion

This review mainly focuses on opportunistic nature of mucormycosis in immunocompromised patients; especially in COVID 19 infected ones. In COVID 19, due to consumption of variety of drugs, physiology of body changes and if patient has to go through the surgery or other medical utilities, these situations create higher chances of infection of mucormycosis. Early diagnosis with proper, effective and safer medication will be proven as greater help to overcome this condition.

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