



## **Mucormycosis - An Indian Epidemic: A Challenge for the Indian Public Health Care System in COVID – 19**

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### **Abstract**

The world was hit by the Coronavirus pandemic, in November 2019, which is believed to have originated in Wuhan, China. The SARS CoV-2 Coronavirus has shown to be a highly pleomorphic virus, which seems to be the key reason for its varying presentations and post-recovery side effects. The traditional virus presentation involves “Flu-like”

respiratory symptoms which usually last for 10-14 days. However, newer presentations with gastric involvement have been recently recorded. Post- recovery a large variety of side effects has been recorded. While a few include minor side effects such as exertional dyspnea, body ache, headache, hair fall, etc., severe side effects such as mucormycosis in both active covid infections

and post-recovery cases have been recorded. The incidence of mucormycosis in post covid - patients has shown an exceedingly high number in the Indian subcontinent, making it a prime concern and challenge for the public health care system in India.

This article emphasizes the association of mucormycosis with covid-19 infections providing a holistic review on its microbiological traits, pathogenic association with covid-19, signs and symptoms, and varying treatment modalities. A holistic review was conducted using databases like Google Scholar, ResearchGate, PubMed and EBSCOhost using keywords like mucormycosis, covid-19, epidemiology available online from the year 1979 to 2021 and retrieving various relevant articles.

### **Keywords**

COVID-19, Pandemic, Mucormycosis, Mucorales, Corticosteroids, Black Fungus, Epidemiology

### **Introduction**

The Covid-19 outbreak caused by SARS-Cov2, creating havoc worldwide is believed to have originated in Wuhan, China.<sup>1,2</sup> The SARS-Cov2, has jumped between the species, causing a zoonotic spread from bats to humans.<sup>3</sup> The infection chiefly spreads via inhalation of infected respiratory droplets, therefore it is essential to maintain personal hygiene and protective barriers with masks, face shields, gloves, etc.<sup>4</sup> It is a highly contagious infectious, that has affected millions worldwide. As of June 2021, more than 180,000,000 cases have been reported worldwide of which nearly 30,000,000 cases have been reported in India.<sup>5</sup> While most patients experience only mild symptoms such as fever, dry cough, fatigue, chills, muscles pain, headache, gastric disturbances, and weight loss,<sup>6</sup> or may even be asymptomatic.<sup>7</sup> However, a large fraction of

patients with respiratory distress has been reported which may lead to multisystem organ failure and death. The rapidly upcoming mutations are often associated with unconventional symptoms. Although maximum people affected with COVID-19 recover within weeks of illness, some of them experience post-COVID conditions. Post-COVID complications are a wide range of new, repeating, or existing health issues that people experience within or after four weeks of being infected with the COVID-19 virus.<sup>8</sup> These include fatigue, headache, difficulty in concentrating (Brain Fog), palpitations, dizziness on standing, persistent cough, muscular pain, etc. In severe cases, multisystem inflammatory syndrome (MIS) has also been reported. Specific pathophysiologic features of COVID-19 are believed to exist which may cause secondary fungal infections, including an affinity to cause extensive pulmonary disease following interstitial lung diseases that may aggravate the risk of invasive fungal infections.<sup>9</sup> Of late, numerous cases have come into light with Covid-19 associated mucormycosis, with an increasingly high incidence in the Indian subcontinent. While the exact cause of the sudden rise in infectious cases remains unclear, numerous hypotheses have been put forward, which include hypoxia, uncontrolled diabetes, metabolic acidosis, diabetic ketoacidosis, high level of ferritin, and reduced phagocytic activity of white blood cells due to immunosuppression linked with various other risk factors including extended hospitalization with or without the mechanical ventilators.<sup>10</sup> High levels of inflammatory cytokines and impaired cell-mediated immune response along with reduced CD4 + T and CD8 + T cell counts have been observed in Covid-19 patients, hence inclining the susceptibility towards secondary infections.<sup>11</sup>

**Mucormycosis in Covid-19**

A multiplex of factors, involving pre-existing comorbidities, such as diabetes mellitus, lung diseases, ongoing corticosteroid therapy, prolonged hospitalization, etc. is known to be associated with risk of nosocomial and other secondary infections as a result of reduced immunity in covid-19 patients.<sup>12</sup> The second wave of Covid-19 in India has had a catastrophic impact on the nation, with the highest daily cases being reported worldwide as of May 2021.<sup>13</sup> As India is continually battling over the current covid crisis, another brewing threat, coronavirus-associated mucormycosis has emerged with at least 14 872 cases as of May 28, 2021.<sup>14</sup> It is potentially fatal and is acquired by a group of moulds called mucormycetes. An increasing number of cases have been reported in the states of Gujarat and Maharashtra.<sup>15</sup> Other states too have shown a steady increase in the number of cases and deaths associated with it, thus declaring it an

epidemic and a notifiable disease to the national health authorities. As of April 2021, nearly 71% of the cases recorded worldwide, have been reported from India.<sup>16</sup>

**Epidemiology of Mucormycosis**

Mucormycosis occurs when people are exposed to the fungal spores in their surroundings. With increasing incidence, various pathogens, and a vulnerable group population, the epidemiology of mucormycosis has changed recently. The increase can be observed globally, but mostly in Asian countries. After inhaling spores, the virus may become evident in the lungs or sinuses. This type of mucormycosis is more common in people with decreased immunity due to health problems. Once the fungus has reached the skin through an incision, scratches, burns, or other types of skin trauma, mucormycosis can develop.<sup>17</sup> Table 1 shows the distribution of cases which were under treatment in different parts of India for mucormycosis as reported on 25<sup>th</sup> May 2021 at 9:36 PM.

**Table 1:** Source<sup>18</sup> Cases Under Treatment In Different Parts of India

States / UT	CASES UNDER TREATMENT AS PER PORTAL ON 25 <sup>TH</sup> MAY 9:36 PM
ANDHRA PRADESH	768
BIHAR	215
CHANDIGARH	83
CHHATTISGARH	103
DELHI	119
GOA	10
GUJARAT	2859
HARYANA	436
HIMACHAL PRADESH	3
JAMMU AND KASHMIR(UT)	5
JHARKHAND	29
KARNATAKA	481
KERALA	36
MADHYA PRADESH	752
MAHARASHTRA	2770
ODISHA	15
PUDUCHERRY	2
PUNJAB	141
RAJASTHAN	492
TAMIL NADU	236
TELANGANA	744
TRIPURA	1
UTTAR PRADESH	701
UTTARAKHAND	124
CENTRAL INSTITUTIONS	592
TOTAL	11717

## **Microbiology**

Mucormycetes, the group of fungi responsible for causing mucormycosis, are present all over the environment, mostly in soil, and are linked with decomposing organic matter, like leaves, compost piles, and animal dung. They are more frequent in summer and fall than in winter or springtime.. Almost all people contact microscopic fungal spores on a day-to-day basis, though most of these fungi aren't harmful to healthy individuals. However people having weak immune systems are at a much higher risk of acquiring such infections by spore inhalation in comparison to normal healthy individuals.<sup>19</sup>

### **Types of Fungi That Cause Mucormycosis**

Several types of fungi can cause mucormycosis. These are called mucormycetes and belong to the hierarchy of Mucorales. The most common types responsible for mucormycosis are the *Rhizopus* species and the *toofToucor* species. Others include *Rhizomucor*, *Syncephalastrum*, *Cunninghamella bertholletiae*, *Apophysomyces*, *Lichtheimia* (formerly *Absidia*), *Saksenaea*, and *Rhizomucor*.<sup>19</sup>

### **Microscopic Features**

In the affected tissue of the extensively necrotic lesion, numerous large, pale-colored, broad, flat, non-septal hyphae with right-angle or obtuse branches are seen. In culture, round or ovoid sporangia are also often observed. Invasive diseases are characterized by large infarcts and angioinvasions, and in cases where nerve structures are affected, there may be a perineural invasion. Angioinvasion is more widely exhibited in neutropenic patients than in non-neutropenic patients. PAS or Grocott Gomori Methenamine Silver Stain are used to highlight fungal hyphae for a more accurate assessment of morphology, while fungal elements are easy to see in cross-sections.<sup>20</sup>

## **Signs and Symptoms of Mucormycosis.<sup>21</sup>**

As per the Indian Council Of Medical Research, the common signs for the diagnosis of mucormycosis includes:

1. Sinusitis
2. Foul-smelling nasal discharge ( blood/black-colored) with headache
3. Unilateral facial pain
4. A localized pain in the cheekbone area
5. Selling and numbness in the cheek area
6. Halitosis in a diabetic patient
7. History of covid-19

Some of the warning signs include:-

1. Blackish discoloration over the bridge of nose/palate
2. Toothache
3. Loosening of teeth
4. Jaw involvement
5. Blurred or double vision
6. Chest Pain and fever
7. Skin lesions
8. Thrombosis and necrosis
9. Pleural effusion
10. Haemoptysis
11. Worsening of respiratory symptoms

Post Covid-19 recovery signs of mucormycosis or black fungus usually begin to manifest within a few days. The infection starts progressing from the sinus to the eyes within two to four days. In the next 24 hours, it spreads to the brain. However, the symptoms differ with respect to the site of the infection. Identification and diagnosis of the infection, as well as timely delivery of effective antifungal therapy, are of prime importance for a good prognosis.

Mucormycosis shows various forms including <sup>21</sup>

1. Rhinocerebral

2. Pulmonary
3. Cutaneous
4. Gastrointestinal
5. Disseminated type

The most common being rhinocerebral and pulmonary.

### **Rhinocerebral Mucormycosis**

Rhino-orbito-cerebral involvement is the primary site of mucormycosis. High morbidity of the infection at this site is due to the fact that by the time the signs and symptoms become apparent, the infection has invaded the deeper tissues causing widespread destruction.<sup>22</sup> Rhinocerebral (sinus and brain) mucormycosis starts from the sinuses and then rapidly progresses to the brain. It is the most commonly encountered presentation of the infection, with an increased prevalence in those with uncontrolled diabetes mellitus, kidney transplants, or leukemia.<sup>23</sup>

Necrosis followed by thrombosis that presents as black necrotic eschars is the hallmark of the disease.<sup>24</sup> The fungi gain entry via inhalation and then may spread to the sphenoid sinus, palate, and cavernous sinus, eventually spreading to the brain. Blurred vision, orbital inflammation, sinusitis, face discomfort or numbness, headache, proptosis, ophthalmoplegia, or even periorbital cellulitis are all common manifestations.<sup>25,26</sup>

Rhinocerebral (sinus and brain) mucormycosis symptoms include:

- face edema on one side
- Headache
- Congestion in the nose or sinuses
- Black spots on the nasal bridge or the upper interior of the mouth that rapidly worsen
- fever<sup>27</sup>

### **Pulmonary (lung) Mucormycosis**

Pulmonary mucormycosis is the next most frequently encountered manifestation seen in covid-19 patients. It is the common type of mucormycosis in people with hematological malignancy with neutropenia and organ transplant or stem cell transplant cases.<sup>23</sup>

Symptoms of pulmonary (lung) mucormycosis include:

- Fever
- Cough
- Chest pain
- Shortness of breath<sup>27</sup>

Diagnosis between invasive aspergillosis and pulmonary mucormycosis is relatively difficult owing to the similarity in symptoms and radiographic features. On chest computed tomography scan, the reversed halo sign, an area of central ground-glass necrosis surrounded by a ring of consolidation, is suggestive of pulmonary mucormycosis.<sup>27,28</sup>

### **Pathogenesis**

The main source of infection is usually inhalation of infected respiratory droplets, from where it spreads further via a hematogenous route along the elastic lamina of the arteries causing thrombosis and infarction.<sup>29,30</sup> Intracranial involvement may occur by invading the superior orbital fissure, ophthalmic vessels, cribriform plate carotid artery, or possibly via a perineural route.<sup>31</sup>

Corticosteroid drugs are routinely used while treating covid infected patients as they reduce the tissue inflammatory response and thereby provide relief from respiratory distress.<sup>32</sup> However, one of the major drawbacks associated with the use of these drugs is lowered host immune response, which is attributed to be a major cause of secondary infections in covid infected patients.<sup>33</sup>

The most severe risk factor is diabetes mellitus, immunosuppressive therapy, leukemias, neutropenias.<sup>34</sup> Some recognized risk factors include patients with neutrophil malfunction, diabetic ketoacidosis, hematopoietic stem cell transplantation, and HIV/AIDS. Patients with elevated serum ferritin levels have an increased susceptibility to mucormycosis owing to their highly angioinvasive nature. *R. oryzae* grows inadequately in normal serum unless exogenous iron is added. Recent epidemiological data have revealed that the amount of accessible, unbound iron in serum shares a direct relationship with the incidence of mucormycosis in DKA patients.<sup>35,36</sup>

People lacking phagocytes or have reduced phagocytic activity are also more vulnerable to mucormycosis. Severely neutropenic patients are at a higher risk of getting mucormycosis. But patients actually with AIDS, on the other hand, are comparatively at lower risk.<sup>37</sup> These data conclude that neutrophils, and not necessarily T lymphocytes, play an important role in preventing fungal spore growth. Additionally, typical host mononuclear and polymorphonuclear phagocytes destroy Mucorales by producing oxidative metabolites and cationic peptides, defensins.<sup>38,39,40</sup> Another recent research found that exposing neutrophils to *R. oryzae* hyphae causes an increase in toll-like receptor 2 expressions along with a strong pro-inflammatory gene expression which increases the activation of NF- $\kappa$ B pathway-related genes.<sup>41</sup> Phagocytes are malfunctioning in hyperglycemic conditions & a low pH, which is observed in diabetic ketoacidosis (DKA) patients, which develop reduced chemotaxis and decreased intracellular death by both oxidative and nonoxidative processes.<sup>42</sup>

### **Predisposing Conditions**

According to various studies, the most essential environment predisposing to mucormycosis are malignant hematological disease in the absence or presence of stem cell transplantation, severe neutropenia, high blood sugar with or without diabetic ketoacidosis, iron overload, severe injury, continuous use of corticosteroids, illicit intravenous drug use, preterm infants & undernourishment.

Voriconazole and caspofungin, two antifungal drugs with little efficacy against Zygomycetes, have also been linked to breakthrough zygomycosis. hospital environment also plays role in the growth of this fungus

Nosocomial mucormycosis has been linked to exposure to high levels of fungal contamination in the atmosphere as a result of continuous construction work, polluted air filters, or a broad range of healthcare-related treatments and gadgets, including infected wound dressings, transdermal nitrate patches, intravenous catheters, tongue depressors, and even allopurinol pills.<sup>43</sup>

### **Treatment**

The key towards the treatment of mucormycosis is directed towards four basic steps:-

- 1) early diagnosis;
- 2) treatment of predisposing conditions ;
- 3) surgical wound debridement,
- 4) Aggressive antimicrobial therapy.<sup>4</sup>

#### **• Early Diagnosis**

According to studies, when treatment is started within 5 days after mucormycosis diagnosis, survival is significantly improved as compared to polyene therapy which starts after  $\geq 6$  days of diagnosis (83% vs 49% survival). As a result, obtaining a timely detection of

mucormycosis is important in order to begin effective antifungal medication as quickly as possible.

The exploration of alternative screening techniques is a significant urgent need for this illness. The establishment of quantitative polymerase chain reaction methods is an exciting area of ongoing research that will allow for faster detection.<sup>17,20,21,22</sup> Because sinusitis has been the most prevalent result of CT scans in individuals with rhino-orbital-cerebral illness, if no underlying infection is seen in the CT scan, that does not exclude out mucormycosis.<sup>23</sup> When identifying CNS and orbital involvement, MRIs are more accurate than CT scans. CT scans can help identify pulmonary mucormycosis early, especially for cancer sufferers.

#### • **Treatment of Predisposing Factors**

In order to improve the overall host defense mechanism, it is imperative to initiate prompt treatment towards the correction of underlying predisposing factors. Immunosuppressive drugs, mainly corticosteroids, should be tapered by dose or terminated if possible. Iron intake should be discouraged because it enhances the infection's severity. Because of the same reason, if at all possible, blood transfusions should be avoided.

#### **Surgical Management**

Some major consequences of mucormycosis are blood vessel thrombosis and tissue necrosis. These lead to poor action of antifungal agents to the infection site. Hence, necrotic tissue debridement is crucial for the absolute eradication of mucormycosis. A recent study suggested that surgery could be an independent variable by logistic regression for a promising result in patients having mucormycosis.<sup>3</sup> Furthermore, in multiple case series, patients who did not undergo surgical debridement of mucormycosis had a far higher mortality rate than patients who underwent surgery.<sup>6,28-</sup>

<sup>35</sup> Although there is potential selection bias in these case series, as patients who did not undergo surgery likely differed in disease severity or comorbidities from those who did, these data favor the concept of surgical debridement to maximize the rate of success to restore health.

#### **First-Line Monotherapy**

Polyene derivatives should be used as the first-line antifungal therapy for mucormycosis. For a great many years, amphotericin B deoxycholate (AmB) was the gold standard for mucormycosis treatment., lipid formulations of Amphotericin B are known to be low on nephrotoxicity and can be given judiciously at higher doses for long as compared to AmB.<sup>23,27</sup> It has the widest anti-fungal spectrum and remains the primary choice of systemic mycotoxins infections. However, with the treatment of liposomal amphotericin B, the survival rate is 67% as compared to conventional AmB, which is 39% when given to patients (p=0.02) [9]. In other recent case studies, LAmB was found to be significantly more effective than other approaches when used as an initial treatment.<sup>14,38,39</sup> As a result, many experts nowadays prefer to treat mucormycosis with lipid-based polyenes instead of AmB.

#### **Prevention of Mucormycosis in COVID-19 Patients**

- Judicious and supervised use of systemic corticosteroids in compliance with current preferred practice guidelines
- Supervised use of tocilizumab in compliance with the current record practice guidelines
- Aggressive monitoring and control of diabetes mellitus
- Strict aseptic precautions while administering oxygen
- Personal and environmental hygiene
- Betadine mouth gargle avoiding nasal drops

- Barrier mask covering the nose and the mouth
- Consider prophylactic oral posaconazole in high-risk patients (> 3 weeks of mechanical ventilation, > 3 weeks of supplemental oxygen. > three weeks of systemic corticosteroids ) uncontrolled Diabetes mellitus with or without ketoacidosis prior to chronic sinusitis and comorbidities with immunosuppression<sup>44</sup>

In immunocompromised patients with a history of mucormycosis and re-encounter of the infection, wide surgical resection and recommencement of the prior effective drug is strongly advised<sup>45</sup>

### **Conclusion**

The rising cases of mucormycosis a.k.a the Black Fungus have shown an even darker side of the already dreaded Covid-19 infection, which continues to challenge healthcare systems across the world. Major challenges include steadily rising superinfections and co-infections such as mucormycosis, which have proven to be fatal. Widespread awareness to allow prompt diagnosis is the major key towards the management of such conditions. Since this disease is associated with high mortality and morbidity, maintenance of optimal health is essential. Uncompromised blood sugar control along with the strategic use of steroids and suitable antimicrobial agents can favor a positive prognosis. Imposing restrictions on over-the-counter sales of systemic corticosteroids and antibiotics should be ensured so as to prevent unauthorized and improper use and hoarding of medications. Early diagnosis; treatment of the prime predisposing factors; surgical debridement (if applicable) and immediate antimicrobial therapy hold the key towards the successful management of mucormycosis.

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