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Mucormycosis in the COVID-19 Era – A Natural Calamity or Man-Made Disaster? Current Evidence and Review of the Literature

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ABSTRACT

Mucormycosis is a potentially fatal disease caused by a fungus of the order Mucorales, most commonly involving the nasal sinuses, orbits, brain, lungs, and skin. The disease affects mostly immunosuppressed individuals and patients with chronic diseases such as diabetes. The prevalence of mucormycosis is 80 times higher (0.14 per 1000) in India compared to developed countries. Since the outbreak of the COVID-19 pandemic, there has been a sudden surge in the number of mucormycosis cases, especially on the Indian subcontinent. This can be attributed to what we consider to be the perfect iatrogenic recipe: a combination between the immunosuppression caused by COVID-19, the large prevalence of uncontrolled diabetes and the simultaneous use of corticosteroids. Other factors include the excessive use of antibiotics, antifungal drugs and zinc supplements, invasive ventilation, poor hygiene and sanitization as well as the use of industrial oxygen in hospitals. As a result, an overwhelmingly large number of COVID-19 patients have developed mucormycosis during the pandemic. A review of the literature suggests that all efforts should be made to keep tight control of glycemia in COVID-19 patients along with judicious use of corticosteroids. The treatment of mucormycosis involves a combination of medical and surgical therapy, with the early initiation of antifungal drugs and aggressive surgical debridement of the affected tissues.

Keywords: mucormycosis, COVID-19, diabetes mellitus, corticosteroids

INTRODUCTION

Mucormycosis is a potentially fatal disease that commonly involves the nasal sinuses, orbits, brain, lungs, and the skin. Rarely, it can even cause disseminated disease. Mucormycosis is caused by a fungus of the order Mucorales, subphylum Mucormycotina. It is highly invasive and relentlessly progressive, resulting in high rates of mortality. The worldwide prevalence of mucormycosis varies from 0.005 to 1.7 per million. In contrast, its prevalence is an astounding 80

times higher (0.14 per 1,000) in India compared to developed countries.[1,2] Put simply, India is the world capital of mucormycosis. Since the outbreak of the COVID-19 pandemic, there has been a sudden surge in the number of mucormycosis cases, especially on the Indian subcontinent. Some other countries, such as Mexico and Russia, also reported an increased incidence of mucormycosis after the COVID-19 outbreak.

MYCOLOGY

Mucormycosis is caused by fungi belonging to the *Rhizopus*, *Mucor*, *Rhizomucor*, *Cunninghamella*, and *Absidia* species. These organisms are present everywhere in nature and are commonly seen in decomposing vegetation in the soil.[3] They breed promptly and release an enormous number of spores, which rapidly become airborne and are transported on long distances. Due to their ubiquitous presence in the environment, the majority of humans have significant exposure to these fungi during their everyday life. However, the fungi seldom cause an infection in humans with a healthy immune system, and the majority of cases occur in an immunocompromised host. The hyphae of these species have a trenchant appearance that helps in the identification of clinical specimens. The hyphae appear thick (5–15 μm diameter) with irregular branching patterns and no septations.

PATHOGENESIS

The disease is acquired through the inhalation of spores. In healthy individuals, the spores are cleared through the gastrointestinal tract. In immunosuppressed individuals, the initial infection starts in the nasal turbinates or the alveoli.[4] The fungi are angio-invasive, leading to infarction of the infected tissues.[5]

There are several factors that increase the risk of mucormycosis. One of them is deferoxamine therapy, which chelates iron and enhances the risk of mucormycosis by accelerating the growth of fungi.[6–8] The deferoxamine-iron chelate, called feroxamine, is a siderophore for the *Rhizopus* species, increasing iron uptake by the fungus, which stimulates fungal growth and leads to tissue invasion.[9] Iron overload independently stimulates the growth of fungi even in the absence of deferoxamine therapy. Also, mucormycosis-causing organisms have a special enzyme called ketone reductase, which helps them to survive in hostile conditions such as high-glucose and acidic environments. A healthy immune system suppresses the growth of mucormycosis-causing organisms, whereas in patients with diabetic ketoacidosis, the growth of *Rhizopus* is accelerated because of this special enzyme.[10] Even in the absence of ketoacidosis, hyperglycemia can directly contribute to the risk of mucormycosis by at least one of the following mechanisms:

- hyperglycation of iron – sequestering proteins, disrupting normal iron sequestration;
- upregulation of a mammalian cell receptor (GRP78) that binds to Mucorales, enabling tissue penetration;
- induction of poorly characterized defects in phagocytic function;
- enhanced expression of cotH, a Mucorales-specific protein that mediates host cell invasion by binding to GRP78 due to hyperglycemia and the resulting free iron.

Risk factors for mucormycosis include:

- diabetes mellitus, particularly when associated with ketoacidosis;
- glucocorticoid treatment;
- hematologic malignancies and hematopoietic cell transplantation;
- solid organ transplantation;
- deferoxamine treatment and iron overload;
- AIDS;
- injection drug use;
- trauma/burns;
- malnutrition.

THE POSTULATED MECHANISM FOR THE SURGE OF MUCORMYCOSIS CASES DURING THE COVID-19 PANDEMIC

SARS-CoV-2 causes lower respiratory tract infection and acute respiratory distress syndrome (ARDS). Besides the diffuse alveolar damage with severe inflammatory exudation, COVID-19 patients also have immunosuppression with a decrease in CD4 and CD8 T cells.[11] A study conducted in 2020 observed that critically ill patients, who were admitted to the intensive care unit (ICU) and required mechanical ventilation or had a longer duration of hospital stay, were more likely to develop fungal co-infections.[12] Other studies have also come to the conclusion that COVID-19 patients can develop fungal infections during the middle and even the later stages of the disease.[13] The number of patients who developed post-COVID mucormycosis was overwhelming. Upon retrospec-

tive analysis of the available data, we observed that the perfect iatrogenic recipe was cooked, which gave birth to a mucormycosis endemic in an ongoing COVID-19 pandemic. Some of the factors that contributed to this surge are listed below.

1. **The very large number of patients with diabetes and prediabetes.** India is the world capital of diabetes; every seventh Indian has either diabetes or prediabetes. According to a study published in The Lancet in 2017, the overall prevalence of diabetes in 15 states of India is 7.3% (95% CI 7.0 to 7.5), with higher levels in urban areas (11.2%, 95% CI 10.6 to 11.8) compared to rural areas (5.2%, 95% CI 4.9 to 5.4).[14] The majority of the population has poor glycemic control, putting them at high risk of mucormycosis. According to a study, 97% of patients who had post-COVID rhino-orbital mucormycosis were diabetic.[15] Another study showed that uncontrolled diabetes was present in 93% of patients who developed rhino-orbital-cerebral infection.[16]
2. **Excessive use of corticosteroids.** The second wave of COVID-19 in India was caused by the Delta strain, which was notorious for severe disease and ARDS. Thus, the number of patients who required corticosteroid treatment was very high. Steroids unmasked the diabetes of this large population and worsened their glycemia, putting them at risk of mucormycosis. According to one study, 80% of patients who had post-COVID rhino-orbital mucormycosis had received steroid treatment.[16]
3. **Unnecessary use of antibiotics.** The majority of the Indian population took unnecessary antibiotics ranging from macrolides to carbapenem, which disturbed their normal flora, predisposing them to mucormycosis.[17]
4. **Unnecessary use of antifungal drugs for prophylaxis.** It has been noted that many centers were using voriconazole for fungal prophylaxis, which increased the risk for mucormycosis.[18] As observed in one study, 6% of patients who developed mucormycosis in India had been given voriconazole for fungal prophylaxis.[16]
5. **Invasive ventilation.** A systematic review of the literature has shown that invasive mechanical ventilation is an important risk factor for invasive fungal infections.[19] As observed in a study, 48% of patients who developed mucormycosis in India had been admitted to the ICU and the majority of them received invasive ventilation.[16]
6. **Poor hygiene and sanitization in hospitals.** Fungal growth in damp buildings is a significant problem. Excess indoor moisture leads to the growth of microorganisms such as molds and fungi. *Penicillium chrysogenum*, *Acremonium*, *Rhizopus*, *Mucor*, and *Aspergillus versicolor* are the most commonly encountered fungal species in water-damaged buildings.[20] There are many hospitals in India with old buildings that have damp walls, increasing the risk of fungal infections.
7. **Excessive use of zinc supplements.** Zinc supplements were used very frequently in the treatment of COVID-19 in India. A study has shown that R. arrhizus isolates grew better with zinc enrichment in vitro, which seems to support the hypothesis that excessive zinc supplementation might have contributed to the pathogenesis of COVID-19-associated mucormycosis.[21]
8. **Oxygen use.** At the peak of the pandemic, there was a shortage of medical-grade oxygen in India, therefore industrial oxygen was used, which was possibly not sterile. Contaminated water used in the humidifier could be another reason for COVID-19-associated mucormycosis. This is just a hypothesis, there is no proven evidence for that to date.

The surge in the number of mucormycosis cases appears to be caused by the intersection of two crises: COVID-19 and poorly controlled diabetes in the setting of the pandemic.

CLINICAL FEATURES

According to a review by Jeong *et al.*, the most common clinical presentations of mucormycosis are rhino-orbital-cerebral (34% of cases), pulmonary (21%), cutaneous (20%), and disseminated infection (14%).[22] In patients with hematological malignancies, the main clinical form of the disease is pulmonary. In India, rhino-orbital-cerebral presentation associated with uncontrolled diabetes mellitus was the predominant clinical presentation, and isolated renal mucormycosis has emerged as a new clinical entity.[23] The most common signs and symptoms of rhino-orbital-cerebral disease include fever, followed by nasal complaints such as blackish discharge from the nose, nasal ulceration or necrosis, periorbital or facial swelling, and ophthalmoplegia (Figure 1). Headache and altered sensorium are more common when the disease infiltrates into the brain. Pulmonary mucormycosis can present as fever, cough, and non-resolving pneumonia usually involving both lungs. Gastrointestinal mucormycosis has non-specif-

FIGURE 1. Rhino-orbital-cerebral mucormycosis

ic clinical presentation, such as dyspepsia and enigmatic diarrhea, and can rarely present as acute peritonitis due to perforation of the gut.

DIAGNOSTIC WORKUP

The diagnosis of mucormycosis is mainly based on histopathology. It can also be confirmed by a positive fungal culture but unfortunately, cultures are seldom positive. Rarely, fungal cultures can even be falsely positive due to the presence of benign mucormycosis-causing fungi in the airways of healthy adults. Therefore, positive cultures should always be correlated with the clinical picture. There is no data regarding the benefits of fungal biomarkers, such as Beta-D-glucan or Galactomannan, in diagnosing mucormycosis. Molecular methods, such as PCR on histopathological samples, are still under investigation, though there are encouraging results from a few recent studies.[24–26] Rhino-orbital-cerebral mucormycosis should be suspected in diabetic patients who have very poor glycemic control or have a history of diabetic ketoacidosis and present with complaints of blackish nasal discharge, proptosis, and ophthalmoplegia, or altered mental sensorium. These patients should undergo an ENT examination with nasal scraping, nasal endoscopy, and histopathology examination of the sample, to look for aseptate hyphae with right-angle branching. The spread of infection to the orbits and the brain can be confirmed by a contrast MRI. The diagnostic workup also includes histopathology and fungal culture from the sputum or bronchoalveolar lavage specimens in case of pulmonary infections, endoscopy and biopsy specimens in case of gastrointestinal infection, and percutaneous kidney biopsy specimens or nephrectomy in case of renal infection.

MANAGEMENT

The treatment of this lethal infection involves a combination of medical and surgical therapies, with early initiation of antifungal drugs and surgical debridement of the affected tissues.[27,28] One of the most important components of treatment is the elimination of all possible risk factors such as acidosis, uncontrolled glycemia, use of immunosuppressive drugs, and neutropenia.

Surgical management

The surgical management of mucormycosis involves the aggressive debridement of the affected tissues, which leads to improved clinical outcomes, especially in rhino-orbital-cerebral infections.[29,30] In some cases, the intervention poses significant challenges because it can lead to a disfigurement of the face due to the removal of vital tissues like the palate, nasal cartilage, and orbit. In case of pulmonary mucormycosis, there is some evidence that early localized infections were cured through lobectomy. However, many patients present extensive pulmonary involvement, and surgery is not possible.

Medical management

Medical management involves the early initiation of antifungal drugs. Amphotericin B is the first-line antifungal therapy of choice, and it is available in three forms: amphotericin B deoxycholate, liposomal amphotericin B, or the amphotericin B lipid complex.[31,32] Due to their better toxicity profile, most physicians prefer liposomal amphotericin B or amphotericin B lipid complex. The initial dose is 5 mg/kg/day, which may be titrated up to 10 mg/kg/day in severe cases.

There are case reports where isolated renal mucormycosis was cured using amphotericin B deoxycholate. The lipid-based preparations are not recommended in renal mucormycosis because they do not penetrate well into the renal tissue. There is no data regarding the effectiveness of combination antifungal therapy. Furthermore, it is not practical to give intravenous injections of amphotericin B for a prolonged period; once the patient becomes stable or is discharged, they can be shifted to oral posaconazole or isavuconazole. Usually, oral posaconazole delayed-release tablets are used. The dose of oral posaconazole is 300 mg every 12 hours on the first day of treatment, and then 300 mg once a day.[33] The target of oral therapy is to achieve trough levels of more than 1 μg/mL after one week of therapy. It is more cumbersome to use isavuconazole due to its complicated loading dose of 200 mg every 8 hours for six doses, followed by 200 mg once daily after 24 hours from the last loading dose. Both oral posaconazole and isavuconazole are tolerated well, with minimal side effects. There is no consensus on the duration of the therapy. In general, most physicians prefer to give antifungals until there is complete resolution of the disease both clinically and radiologically. Usually, antifungals are given for months and rarely lifelong in patients whose immunosuppression cannot be rectified.

PROGNOSIS

In general, the prognosis of mucormycosis is poor, with the rare exception of cutaneous involvement. Risk factors for mortality include disseminated infection, persistent organ failure, and infection with the *Cunninghamella* species. Patients with infection confined to the sinuses have the best prognosis, while mortality from rhino-orbital-cerebral mucormycosis ranges from 25% to 62%.3 In patients with pulmonary mucormycosis, the prognosis is even worse, with mortality rates as high as 87%.

CONCLUSIONS

A combination of uncontrolled diabetes and simultaneous use of corticosteroids is a major risk factor for the surge of mucormycosis in COVID-19 patients. All efforts should be made to keep tight control of glycemia in COVID-19 patients along with judicious use of corticosteroids. The treatment of mucormycosis involves a combination of surgical debridement of involved tissues and antifungal therapy.

CONFLICT OF INTEREST

Nothing to declare.

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