

COVID-19 and Mucormycosis: Predisposing Factors and Preventive Strategies

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ABSTRACT

Coronavirus disease-2019 (COVID-19) is caused by severe acute respiratory syndrome coronavirus-2. COVID-19 has been associated with a wide range of opportunistic infections, viz. bacterial and fungal. Mucormycosis is one of the most deadly and life-threatening invasive fungal infections which has typically seen a rising trend with the rise in COVID-19 cases. Patients who are at higher risk to develop mucormycosis include those with uncontrolled diabetes mellitus, steroid-induced immunosuppression, acquired immunodeficiency syndrome, immunosuppression due to malignancies or posttransplant, prolonged stay in intensive care units, patients on oxygen therapy and/or mechanical ventilation, etc. Preventive strategies for mucormycosis should aim at addressing the underlying risk factors in COVID-19 patients, airborne infection control at the facility level, as well as personal protective measures at the individual level. Finally, a high index of suspicion, clinically, on the part of the treating physician can go a long way in prompt diagnosis and initiation of aggressive antifungal therapy and extensive surgical management of mucormycosis, leading to an improved outcome.

Keywords: COVID-19, Diabetes mellitus, Mucormycosis, Opportunistic infection.

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INTRODUCTION

Coronavirus disease-2019 (COVID-19) is caused by severe acute respiratory syndrome coronavirus-2. Worldwide, it has been estimated that more than 204 million cases of COVID-19 infection have occurred as of August 12, 2021.¹ There have been numerous changes in the spectrum of COVID-19 with regard to its diagnosis, management, prevention, complications, and post-COVID sequelae since the emergence of the first case in Wuhan, China, in December 2019.² Of late, COVID-19 has been associated with a wide range of opportunistic infections, viz. bacterial and fungal. Mucormycosis is one of the most deadly and life-threatening invasive fungal infections which has typically seen a rising trend with the rise in COVID-19 cases.³⁻⁵

Mucormycosis is a rare but serious fungal infection caused by a group of molds called Mucormycetes. It most commonly affects the sinuses or the lungs but can also affect the skin post any injury or burn. It usually presents with a blocked nose, facial edema or pain, headache, and proptosis, with a black eschar being seen in the nasal cavity or palate. At times, with intracranial involvement, neurological signs and symptoms may be seen.⁶⁻⁹

Recently, an increasing number of cases of mucormycosis has been reported among COVID-19 cases, especially from India. Higher mortality rates are reported with orbital and intracranial complications with rapid progression if diagnosis and treatment are delayed. Untreated mucormycosis is almost always fatal.¹⁰ A high index of suspicion for prompt diagnosis is required. An aggressive treatment strategy combining both medical and surgical management is often needed; however, sometimes, even this does not suffice.¹¹

WHO ARE AT RISK FOR DEVELOPING MUCORMYCOSIS?

Patients who are at higher risk to develop mucormycosis include those with uncontrolled diabetes mellitus, steroid-induced immunosuppression, acquired immunodeficiency syndrome, immunosuppression due to malignancies or posttransplant, prolonged

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stay in intensive care units, patients on oxygen therapy and/or mechanical ventilation, etc.

DIABETES MELLITUS AND MUCORMYCOSIS

Poorly controlled diabetes mellitus is said to be an important risk factor for mucormycosis.¹² It is also found to rise morbidity and mortality in the context of COVID-19.¹³ It has been reported that COVID-19-associated mucormycosis is classically seen in uncontrolled or poorly controlled diabetics.¹⁴ Also, COVID-19 leads to a diabetogenic state by causing damage to the pancreatic islets, and also cytokine storm is associated with higher insulin resistance.^{15,16} A high index of suspicion is the need of the hour, if any diabetic patient with COVID-19 develops nasal, orbital, or neurological signs and symptoms or presents with these complaints post-COVID-19; it has to be immediately addressed.

DRUG THERAPY AND MUCORMYCOSIS

Steroids have been used extensively in COVID-19 management especially in hypoxemic patients and have also been shown to reduce mortality among them. Corticosteroid therapy, short

or long term, is a risk factor for opportunistic infections like mucormycosis.^{17–19} Thus, judicious use of steroids is recommended in COVID-19 infection and it must be avoided in asymptomatic or mild cases without any hypoxemia. The use of immunomodulatory drugs viz. tocilizumab in COVID-19 patients can increase the risk of secondary infections as the viral infection itself leads to immune dysregulation.^{18,20} Voriconazole therapy is used to prevent opportunistic fungal infections that can sometimes lead to mucormycosis as it is not effective against Mucorales.²¹ Also, indiscriminate use of broad-spectrum antibiotics can lead to increased rates of mucormycosis and needs to be curbed.

MECHANICAL VENTILATION, INTENSIVE CARE SUPPORT, AND MUCORMYCOSIS

It has been observed that patients with COVID-19 requiring mechanical ventilation, oxygen support, and ICU care have higher rates of development of secondary infections including mucormycosis.^{22–24} Invasive procedures like tracheostomy have been associated with an increased risk of secondary infections.²³ Oxygen humidifiers, especially the reusable ones, can lead to increased aerosol transmission of hospital-acquired pathogens. Disposable oxygen humidifiers are therefore advisable.²⁵ It is also recommended to use clean distilled water in oxygen humidifiers, even for home use.

MANAGEMENT OF MUCORMYCOSIS ASSOCIATED WITH COVID-19

A high index of clinical suspicion is needed to diagnose mucormycosis at an early stage and initiate a prompt and aggressive medical and surgical management protocol.

Warning signs and symptoms in COVID-19 patients which should not be ignored are as follows:²⁶

- **Mucormycosis of nose/sinus:** Headache and nasal obstruction, pain not responding to analgesics, nasal crusting and discharge, loss of sensation or pain in the face, localized puffiness of the face, loosening of teeth or ulceration of the palates, etc.
- **Mucormycosis of eyes:** Redness or eye pain and swelling, double vision, loss of vision, drooping of eyelids, etc.
- **Mucormycosis of brain:** Cranial nerve palsies, altered sensorium, etc.

Basic principles for treatment that need to be followed are as follows:²⁶

- Controlling hyperglycemia
- Treatment of comorbidities
- Continuing treatment of COVID-19 and avoiding immunosuppression
- Evaluating the progression of mucormycosis for ocular or intracranial involvement
- Confirmation of diagnosis by KOH mount or biopsy; assessing disease progression radiologically
- Initiation of antifungal therapy: Liposomal amphotericin B or posaconazole
- Aggressive surgical management: Surgical debridement of the necrotic tissue

Liposomal amphotericin B is the drug of choice along with extensive surgical debridement of the infected area and has been shown to improve survival rates. Posaconazole can be used as an

alternative antifungal agent.^{27,28} Delay in the diagnosis or treatment can be detrimental to the outcome and may cause fatalities. Various factors like prompt diagnosis and treatment, type of mucormycosis, immune status of the patient, etc., can determine the prognosis and outcome of the patient.²⁹

PREVENTIVE STRATEGIES FOR MUCORMYCOSIS IN COVID-19

Multidimensional strategies can be implemented for the prevention of mucormycosis in COVID-19. These strategies should aim at addressing the underlying risk factors in COVID-19 patients, airborne infection control at the facility level, as well as personal protective measures at the individual level.

- **Addressing the risk factors:** The underlying factors which can predispose to the development of mucormycosis should be addressed promptly in all COVID-19 patients. These include controlling hyperglycemia, judicious use of corticosteroids, rational use of antibiotics, antifungals, and immunomodulatory drugs, minimizing hospital stay, use of disposable oxygen humidifiers, etc.^{28,29}
- **Infection prevention and control at the facility level:** It is mandatory to have infection prevention and control measures in place at all COVID-19 treatment facilities in order to eliminate the environmental spread of the infection. The following measures can be taken at the hospital level: Regular disinfection and sterilization of hospital equipment like tracheal tubes, oxygen humidifiers, ventilators, etc.; adequate ventilation system; proper wound management; appropriate peripheral and central line management, etc.^{29,30}
- **Personal protective measures:** Cases of mucormycosis have been found to occur among recovered COVID-19 patients as well. Hence, the role of personal protective measures cannot be neglected. These include maintenance of personal hygiene, avoiding construction sites or use of face masks when visiting dusty places, avoidance of contact with soil or use of gloves, shoes, and full-length clothing, avoiding injuries to the skin, etc.³⁰

In conclusion, although various strategies have been outlined for the prevention of mucormycosis among COVID-19 patients, a high index of suspicion, clinically, on the part of the treating physician can go a long way in prompt diagnosis and initiation of aggressive antifungal therapy and extensive surgical management of mucormycosis, leading to an improved outcome.

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