



## Mucormycosis COVID-19 Coinfection

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### Abstract

In the recent past, rhino-orbital mucormycosis in people with COVID-19, were reported from many parts of the world. Diabetes mellitus, though, happens to be an independent risk factor both for severe COVID-19 and mucormycosis, administration steroids is attributed as a precipitating factor for acquiring this comorbid condition. Fungal agents causing mucormycosis are highly angioinvasive in nature, as a result of which, clinical outcome of infection is invariably poor, especially with rhinocerebral or rhinoorbitocerebral variety. Effective management depends upon timely and accurate diagnosis, and parenteral administration of amphotericin B. Judicious use of steroids is always recommended. Glycemic control in those who are severely diabetic is advocated. Surgical debridement of the paranasal sinuses and orbital cavities and removal of dead tissue is an essential part of management in order to facilitate faster healing and better penetration of antifungal drugs. Exenteration of eye ball may be indicated, if cavernous sinus and intracranial spread are anticipated.

**Keywords:** COVID 19, mucormycosis, antifungal drugs, cavernous sinus

### Introduction

COVID-19 caused by the recently emerged severe acute respiratory syndrome coronavirus 2 (SARS CoV 2), manifests clinically as fever, shortness of breath, cough, headache, which can lead to severe pneumonia, lung injury, and acute respiratory failure (Song *et al.*,2020, Rahayu S *et.al* 2021, Chatki, P. K.*et al.* 2021). Corona viruses are non-segmented, enveloped and positive sense single-stranded RNA viruses. They have a genome size ranging from 26 to 32 kilobases( Bhattacharya S *et.al.*,2020). COVID -19 per se and its rapid transmissibility have had a negative impact on family and health (Hasinuddin M. *et.al.*, 2021, Bhattacharya S.*et al.*,2021, Wijaya, M. *et al.*,2022). Fungal infections, such as aspergillosis and invasive candidiasis, were reported in patients with severe COVID-19 or those recovering from the disease. However, recent reports of increasing number of mucormycosis cases among patients with COVID-19 with serious life threatening clinical presentations were alarming (Singh *et al.*,2021).

### Mucormycosis

Mucormycosis is an acutely fatal angio-invasive infection caused by a group of fungi belonging to the order *Mucorales*. Spores of these fungi are ubiquitous, and gain entry to human host via inhalation, leading subsequently to invasion not only of the lung tissue, but of the paranasal sinuses, orbit, blood stream and brain as well (Chander *et al.*, 2018).

Mucormycosis mainly affects people who are immunocompromised i.e those with severe uncontrolled diabetes, especially with diabetic ketoacidosis; solid organ and bone marrow transplant recipients; neutropenic individuals; those on long-term systemic corticosteroids; and persons living with

HIV/AIDS (Prakash *et al.*, 2019). Clinically, patients present with classical signs and symptoms according to the organ involved. Thus, mucormycosis can be of various clinical forms, namely rhino-orbito cerebral, pulmonary, gastrointestinal, cutaneous, or disseminated mucormycosis (Prakash *et al.*, 2019).

#### *Mucormycosis and COVID-19*

The pathophysiological features of severe COVID-19 are dominated by an acute pneumonic process with extensive radiologic opacity and, on autopsy, diffuse alveolar damage, inflammatory infiltrates, and microvascular thrombosis (Horby, P *et al.*, 2021). Recent emergence of Mucormycosis among COVID-19 patients globally, is of concern. Are there any clues to establish a causal relationship between COVID-19 and superadded infection due to *Mucor* or other related fungi of the *Mucorales* group.

First of all, severity of COVID-19 is directly related to the underlying host inflammatory response. It was observed that there was an exaggerated and heightened proinflammatory response, called cytokine storm in patients with severe COVID-19. This dysregulation between Th1 and Th2 cytokines, and the host response tilting more in favor of Th1 type of response, rather than of Th 2 type is responsible for tissue injury (Parlman *et al.*, 2005).

Thus many clinicians advocate administration of steroids to their patients in order to combat the cytokine storm. It was noted in the recent past that steroids were prescribed in quantities and for durations that far exceeded the WHO recommended dosage, which was very likely to compromise patients' immune system, increase blood sugar levels, thus, predisposing the patients to be susceptible to invasive fungal infection (Arora K., & Panda PK., 2021).

#### *Therapeutic challenges*

It is important to note that steroids should be prescribed only when patient is hypoxic with a substantial decline in oxygen saturation. But so long as the status of oxygen saturation is within normal limits, and the patient is having no other symptoms, except fever, dry cough, malaise and mild joint pain, it is unnecessary to go with steroid treatment. At the same time it is true that dexamethasone was shown to be beneficial in certain groups of COVID-19 inpatients. Thus, it should always be kept in mind that, in spite of its benefits, it can potentiate invasive mold infections. Sometimes use of immunosuppressants to combat COVID-19 also increases the risk to get infected with mucormycosis (Choudhary, N. K *et al.*, 2021) Besides, corticosteroids are known to induce hyperglycemia, which will be in addition to the already present high blood glucose because of undiagnosed diabetes associated with COVID-19 cases (Horby P *et al.*, 2021 & Hoeningl H *et al.*, 2022). It was also documented that patients with severe diabetes and hyperglycemia often exhibited a state of inflammatory process that included constant recruitment and activation of macrophages and neutrophils secreting abundant amount of proinflammatory cytokines and generating persistent inflammation (Morales-Franco B *et al.*, 2021).

Therefore, in the event of any indication for steroid therapy, the drug should always be prescribed in the recommended dosage i.e. 6 mg/kg body weight/day of dexamethasone for a maximum period of 7-10 days (Ketensi I *et al.*, 2011). Neither the dose nor the duration of therapy should be compromised.

The treatment of mucormycosis with an underlying SARS-CoV-2 infection is more or less similar to other risk groups with this invasive mycosis. However, treatment of mucormycosis in patients of COVID-19 generally has fewer issues in relation to neutropenia management as observed in patients with hematological malignancies. Nevertheless, management is more focused on diabetes and corticosteroid exposure.

The key elements in the treatment of mucormycosis COVID-19 coinfection are: control of the underlying disease and/or risk factors, surgical debridement of necrotic infected tissue in the paranasal sinuses and orbit in order to facilitate rapid healing and faster drug penetration, and specific

antifungal therapy (Cornely OA *et al.*, 2019). First of all, it is important to carefully control hyperglycemia and make a rapid correction of any ketoacidosis. From a mucormycosis standpoint, the reduction and elimination of prolonged high-dose corticosteroids, if present, should be considered. Administration of antifungal drugs is as important as surgical removal of dead tissue or organ. The most preferred antifungal agent which would take care of *Mucorales* is Liposomal Amphotericin B in a dosage of 5-10 mg/kg/day intravenously (Roden MM *et al.*, 2005 & Lanternier F *et al.*, 2008 ). Such high dose can be administered safely as this formulation of Amphotericin B is devoid of any nephrotoxicity or hepatotoxicity, unlike Amphotericin deoxycholate. However, only disadvantage is that it is an expensive drug, and sometimes it may be beyond the affordable reach of many patients in developing countries.

Amphotericin B deoxycholate, on the other hand, is cheap. It is given in a lower dosage, i.e. 1-1.5 mg /kg /day by slow intravenous (IV) infusion along with 5% dextrose solution. Constant monitoring of renal parameters is important while the patient is on amphotericin B deoxycholate. After clinical improvement, IV therapy is discontinued and the patient is put on oral antifungals like isavuconazole for a period of another 3-4 months (Cornely OA *et al* 2019 & Perfect JR *et al.*, 2018). It may be mentioned here that drugs such as fluconazole, voriconazole or echinocandins are ineffective against mucormycosis.

Before concluding, it will be appropriate to mention here a bottom line truth about fungi causing mucormycosis. Naming these fungi as 'black fungi' is a misnomer. Truly, the term "black fungi" is applicable to a group of fungi, called dematiaceous fungi, which have the inherent property of producing black pigments. The dematiaceous fungi consist of the genera *Alternaria*, *Curvularia*, *Bipolaris*, *Helminthosporium* etc., which are soil saprophytes, but can cause fungal keratitis if their spores are accidentally inoculated on to abraded cornea, after minor trauma with vegetative matter; mainly among farmers and other agricultural workers. However, the dark brown lesions seen in mucormycosis, especially in the nose, paranasal sinuses, and hard palate, due to the high angioinvasive property of *Mucorales* group of fungi, may be reason for these fungi to be named as "black fungi" by certain sectors.

## Conclusion

Mucormycosis and COVID-19 coinfection can be life threatening if a patient of COVID-19 has underlying uncontrolled diabetes with diabetic ketoacidosis. The treating clinician is often faced with diagnostic as well as therapeutic challenges. The complex interplay between *Mucor* and other related fungi of the *Mucorales* group and COVID-19 virus is still not well understood. A multidisciplinary approach involving clinical microbiologist, otorhinolaryngologist, ophthalmologist, and physician is needed for fruitful management of cases.

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