



Mucormycosis in COVID-19 patients: predisposing factors, prevention and management

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Abstract

India is considered the diabetes capital of the world and has the highest burden of mucormycosis. Bacterial, viral and fungal co-infections are increasingly being reported in severe acute respiratory syndrome virus 2 (SARSCoV-2) infected patients. India is one of the worst affected countries during the second wave of the COVID-19 pandemic. This combination of diabetes mellitus, COVID-19 and mucormycosis has led to the drastic upsurge of COVID-19-associated mucormycosis (CAM) in India. Immunosuppression, iron disequilibrium, endothelial injury, ketoacidosis and hypoxia are some of the other COVID-19-related risk factors for CAM. There has been an increase in the proportion of mucormycosis affecting paranasal sinuses and central nervous system (CNS) in CAM compared to pre-COVID-19 literature due to the SARSCoV-2-related pathophysiological mechanisms, complications and treatment strategies. CAM is a medical and surgical emergency, and it can present with non-specific symptoms and signs initially resulting in diagnostic delay. High index of suspicion and regular screening for features of CAM are of paramount importance to prevent lethal consequences. Rapid action with a tripod approach consisting of withdrawal of immunomodulators, early antifungal therapy and extensive surgical debridement is considered the best possible treatment model. We review the published data to give a detailed account of the predisposing factors and their mechanisms, diagnostic work-up, treatment modalities and prevention strategies of CAM with special emphasis on CNS mucormycosis.

Keywords Mucormycosis · COVID-19 · Fungal infection · Diabetes mellitus · Immunosuppression · Amphotericin · Surgical debridement

Key Messages

SARSCoV-2 related pathophysiological mechanisms, complications and treatment strategies can predispose patients to infection with mucormycosis, predominantly affecting paranasal sinuses and CNS.

Hyperglycemia, ketoacidosis, blunted immune response, iron disequilibrium, endothelial injury, irrational use of antibiotics and immunomodulators are the major contributing factors.

Early diagnosis, aggressive medical and surgical management are critical to reduce morbidity and mortality.

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Introduction

The coronavirus disease 2019 (COVID-19) pandemic, caused by severe acute respiratory syndrome virus 2 (SARSCoV-2) since its origin in Wuhan has affected more than 189 million people worldwide, accounting for over 4 million deaths by July 2021. India is one of the worst affected countries, especially by the second wave of the pandemic. The lockdown policies, declining demand and supply for goods and services in addition to increased health-care consumption have led to a global economic crisis [1]. Many treatment

decisions, especially concerning the patients hospitalized with COVID-19, have been made based on limited clinical experience and scientific evidence. Antibiotic therapy in patients with COVID-19 was one such clinical decision. Bacterial, viral, or fungal co-infections are described with COVID-19 even though not to the same extent as that in pandemics caused by influenza viruses [2, 3]. Invasive fungal infections were reported in multiple studies [4, 5] with an incidence of up to 25% in critically ill patients with moderate to severe acute respiratory distress syndrome (ARDS) caused by SARS-CoV-2 [6]. There has been a surge in mucormycosis in patients affected by COVID-19, leading to disabling morbidity, mortality and an additional burden on health economy. We discuss the predisposing factors, potential steps for prevention and treatment aspects of COVID-associated mucormycosis (CAM).

Mucormycosis and COVID-19

Mucormycosis is an angioinvasive fungal infection, with high morbidity and mortality caused by Mucormycetes which belongs to the order Mucorales and class Zygomycetes. Mucorales are thermotolerant saprophytic fungi found in decaying organic matter and soil samples. Pathogenic species such as *Rhizopus*, *Lichtheimia*, *Cunninghamella*, *Rhizomucor* and *Apophysomyces* were documented to be isolated in Indian soils [7]. The fungal spores can gain entry through inhalation, ingestion of contaminated food, or abraded skin resulting in rhino-orbito-cerebral, pulmonary, gastrointestinal, or cutaneous/wound infections [8, 9]. Rhino-orbito-cerebral mucormycosis (ROCM) is the most common form of the disease in India, followed by the pulmonary and cutaneous types. *Rhizopus oryzae* is the most common type, responsible for nearly 60% of mucormycosis cases in humans and 90% of the ROCM form [10, 11]. In ROCM, nasal turbinates are the initial sites to be affected. In a host with intact immune system, the ciliary system helps in the elimination of the spores and phagocytosis can effectively limit the infection and invasion. In an immunodeficient host with inadequate phagocytosis, the spores can germinate into hyphae and invade the vasculature resulting in tissue infarction and necrosis involving the palate, orbit and brain due to contiguous spread [12].

The global prevalence of mucormycosis ranges from 0.005 to 1.7 per million population, while its prevalence in India is nearly 80 times higher (0.14 per 1000) compared to developed countries, making India the country with the highest burden of mucormycosis [13–15]. It constituted 2.7% of all the fungal infections affecting central nervous system (CNS), treated at a tertiary care center in South India [16]. There are increasing reports of rhino-orbital mucormycosis in people with COVID-19, especially in India, in

addition to several anecdotal reports in the print and electronic media [17]. These findings are of immense importance considering the very high case fatality rate, especially with intracranial involvement of mucormycosis, reaching up to 90% [18]. The initial clinical manifestations are often non-specific compounded with early rapid dissemination and clinical worsening, making early clinical suspicion and diagnosis valuable. Nearly 50% of cases of mucormycosis have been historically diagnosed only in the post-mortem autopsy series, suggesting that even a delay of 12 hours in the diagnosis could be fatal [19]. Susceptible COVID-19 patients should be screened regularly for features like headache, nasal obstruction (especially if persistent or severe and not responding to pain medicines), nasal crusting, nasal discharge which could be brownish or blood tinged, pain, loss of sensation or discoloration of skin over the face, localised facial puffiness, loosening of teeth, discoloration or ulceration of the palate, eye pain, swelling or redness, double vision or loss of vision and drooping of eyelid.

Predisposing factors

Mucormycosis is rarely reported in healthy individuals; it is predisposed by comorbidities such as diabetes mellitus, organ transplantation, malignancies (especially hematological), immunosuppressive therapy including corticosteroids, prolonged neutropenia, iron overload, chronic antibiotic use, severe burns, intravenous drug abuse and malnutrition, leading to immunocompromise [20]. Some of these factors are particularly relevant in patients with COVID-19 due to its pathophysiological mechanisms and treatment measures.

Diabetes mellitus (DM)

India is considered as the diabetes capital of the world with around 77 million adults affected [21]. Poorly controlled DM increases the risk of infections due to its effect on host immunological response with significantly increased hospitalization and mortality rates [22]. Mucormycosis is reported to be higher in patients with severe COVID-19 infection and both are predisposed by DM. The presence of DM was associated with increased severity of COVID-19 infection and higher mortality [6, 23]. SARS-CoV-2 infects the host by tropism to host angiotensin-converting enzyme-2 (ACE2) receptor. Increased ACE2 receptor expression, hyperglycemia favoring SARS-CoV-2 replication, dysregulated immune response, coagulopathy, and alveolar and endothelial dysfunction are some of the pathological mechanisms noted in DM resulting in severe infection [24]. Overexpression of GRP78 (glucose-regulated protein), augmented availability of micronutrients, diminished defense mechanisms, and acidic environment (especially in diabetic ketoacidosis

[DKA]) with increased availability of iron for the pathogen make DM the most common risk factor (noted in 54–76% of cases) for mucormycosis. Overexpression of GRP78 is noted specifically in nasal epithelial cells, which can explain the occurrence of ROCM more in patients with DM than those without [9, 25, 26]. Studies in the context of DKA have shown that CotH3 (a protein kinase expressed during sporulation) is mainly expressed in the germinations of *Rhizopus oryzae*. CotH3 has a greater ability to adhere and invade endothelial and nasal epithelial cells compared to other CotH [26].

Systemic reviews have shown that most of the reported cases of mucormycosis in patients with COVID-19 are from India (70–80%), which is not surprising considering the burden of mucormycosis and DM in India [17, 27]. Hyperglycemia at presentation was the single most important risk factor observed in 83.3% of the patients with mucormycosis and COVID-19, pre-existing DM in 80% and concomitant DKA in 15% [17]. Studies have shown that SARSCoV-1 can damage pancreatic islets and result in acute diabetes and DKA [28]. There is also evidence for long-term damage to pancreatic beta-cells by SARSCoV-2 as suggested by the persistence of hyperglycemia and occurrence of DKA long after recovery [29, 30]. A UK study has shown that prevalence of DM and DKA are higher in patients with COVID-19 compared to the general population [31]. Insulin resistance due to cytokine storm and damage to pancreatic islets caused by SARSCoV-2 in addition to use of corticosteroids appear to be the possible explanation for this hyperglycemic state [32].

Blunted immune responses

In addition to DM, several other factors affect the defense mechanisms against opportunistic infections in patients with COVID-19. Lymphocytopenia has been described in severe cases of COVID-19, and it has been hypothesized that the pathological pathway of SARSCoV-2 predominantly affects T cells (CD4+ and CD8+) [33]. Cell-mediated immunity involving Mucorales specific T cells plays an important role in controlling invasive infection through various cytokines (interleukin [IL] 4, IL-10, IL-17 and interferon-gamma) that damage the fungal hyphae, indicating that severe COVID-19 infection by itself is a risk factor for invasive mucormycosis.

Immunomodulators including corticosteroids, monoclonal antibodies against IL-6 receptor such as tocilizumab and sotrovimab, and JAK inhibitors such as baricitinib and tofacitinib are used in the treatment of moderate to severe COVID-19 infections to blunt the exaggerated immune response [34–36]. The frequent use of immunosuppressants along with other predisposing factors provide an ideal environment for invasive fungal infections. In addition, corticosteroids can affect glucose homeostasis resulting in uncontrolled hyperglycemia and precipitation of DKA.

Ketoacidosis creates an ideal environment for germination of fungal spores and reduced cell-mediated immune responses (phagocytic activity), both due to corticosteroids and hyperglycaemic state, further worsen the situation resulting in invasive mucormycosis [24, 37].

Iron disequilibrium and role of zinc excess

Severe COVID-19 infection is characterized by excessive release of cytokines and a hyperferritinemic state. Excessive ferritin synthesis along with reduced extracellular iron transport results in high levels of intracellular iron [38]. Patients with DKA also have elevated levels of free iron in serum, probably due to the release of iron from binding proteins (like transferrin) in the presence of acidosis [37]. Elevated intracellular iron levels in turn produce excessive reactive oxygen species which cause tissue damage and release of free iron into the circulation. The acidic state can be further worsened by renal dysfunction and hypoxia which are common in hospitalized patients with COVID-19 [39]. Evidence shows that elevated levels of serum free iron levels and low levels of dialyzable inhibitory factor in diabetics are suitable conditions for fungal replication. Hence, the acidic milieu (which is the overall effect of multiple factors) forms an ideal environment for fungal proliferation due to the availability of free iron which is required for cell growth and development [37, 40, 41].

Zinc-binding proteins act as transcription factors for biological processes responsible for fungal growth and studies have shown that zinc starvation induces biological stress and inhibits fungal proliferation [42, 43]. Use of micronutrient supplements, including zinc as possible immune boosters has increased in the COVID-19 era, which can contribute to the increased cases of mucormycosis.

Endothelial injury

Endothelialitis and endothelial damage noted in severe COVID-19 forms another possible explanation for increased incidence of mucormycosis. Pulmonary vascular endothelial cells express ACE2 receptors and endothelialitis can be solely immune mediated or due to an immune response secondary to direct viral infection. Autopsy reports in COVID-19 patients have shown severe endothelial injury with disrupted cell membranes, widespread thrombosis, microangiopathy and angiogenesis in pulmonary vasculature along with the presence of intracellular virus [44, 45]. Endothelial adhesion and penetration are critical in the early stages of infection in mucormycosis [41]. Glucose-regulated protein (GRP 78) and the Mucorales adhesin spore coat protein homologs (CotH) are endothelial receptors which facilitate the endothelial adhesion in mucormycosis. Acidosis and

hyperglycemic states induce the expression of these receptors, further worsening the situation [41, 46].

Excessive and irrational use of antibiotics in patients with COVID-19 is underreported. An interrupted time series analyses of sales volumes of antibiotics in India estimated that COVID-19 likely contributed to 216.4 million excess doses of antibiotics and 38.0 million excess doses of azithromycin until the peak of the first pandemic wave [47]. Chronic antibiotic use by itself is a risk factor for opportunistic fungal infections including mucormycosis and irrational use can result in emergence of antimicrobial resistance [48]. A study performed at a tertiary care center in South India compared the risk factors among CAM and non-COVID mucor patients. Most patients (76.7%) with CAM had mild COVID-19. DM was a significant risk factor in both groups, whereas uncontrolled DM and newly detected DM were more common among CAM group. Unwarranted steroid use and elevated serum ferritin levels were found to be significantly higher in CAM patients [49].

Mucormycosis of oronasal cavity or paranasal sinuses can present with symptoms of sinusitis or periorbital cellulitis, facial numbness, conjunctival suffusion, visual blurring, and soft tissue swelling followed by eschar formation and necrosis. Paranasal sinuses are the most common site affected by mucormycosis [50] and the proportion of patients with involvement of paranasal sinuses and CNS has increased in COVID-19-associated mucormycosis compared to pre-COVID studies (Table 1) [17, 51]; this is probably due to pathophysiological mechanisms and complications of SARS-CoV-2.

Central nervous system infection

Incidence and modes of spread

CNS mucormycosis is the third most common site of infection after paranasal sinuses and orbit in the Indian population where DM is the most important risk factor [50]. In a study by Roden et al., DM and injection drug abuse were found to be the most important risk factors for CNS

Table 1 Comparison of the locations of mucormycosis involvement in the non-COVID and COVID-19 patient groups

Location of mucormycosis	Roden et al. [51] (non-COVID) (%)	Singh et al. [17] (COVID) (%)
Sinuses	39	88.9
Cerebral	9	22.2
Pulmonary	24	7.9
Cutaneous	19	1

Bold signifies increase in the COVID group compared to the non-COVID group of patients

mucormycosis. Of 337 mucormycosis patients with DM, 66% had disease of the paranasal sinuses, and 43% of these had cerebral extension [51]. CNS involvement occurs most commonly due to contiguous spread from paranasal sinuses or orbit (70%); other modes include hematogenous spread or direct inoculation (surgery, penetrating trauma, lumbar puncture, epidural injection) [51].

Clinical presentation

CNS mucormycosis can present with features of meningitis, cranial neuropathies (predominantly ophthalmoplegia), other focal neurological deficits and/or features of raised intracranial pressure [52]. Cavernous sinus can be involved, particularly in the course of ROCM leading to thrombosis and cranial nerve dysfunction. Hemiparesis, dysarthria, altered sensorium and focal seizures indicate invasion of brain parenchyma resulting in granulomatous lesions, abscess formation or stroke due to angioinvasion [52–55].

Imaging features

Frequent imaging findings in intracranial mucormycosis include cavernous sinus thrombosis, brain infarction, internal carotid artery occlusion, and parenchymal lesions (granulomatous and abscesses). Lesions may be either hypo- or hyperintense on T2-weighted sequences and diffusion-weighted imaging (DWI) sequences show reduced diffusion [56, 57]. Granulomatous lesions are usually noted in the frontal lobes and affinity of mucormycosis for basal ganglia with abscess formation has been reported in intravenous drug abusers [54, 55].

Diagnosis

The initial symptoms in mucormycosis can be non-specific and can be erroneously attributed to COVID-19 disease itself. There must be a high index of suspicion, especially in patients with predisposing factors. Early warning signs and symptoms should not be missed, as delay in treatment can be fatal.

Laboratory investigations can help to detect hyperglycemia, ketoacidosis, neutropenia, dyselectrolytemia and iron overload states. Computed tomography (CT) scan of the head can show the nature and extent of involvement of the soft tissue structures, sinuses, orbit and brain. Imaging should be thoroughly examined for mucosal thickening and opacification of the sinuses, edema, inflammation and infarcts in the brain, bony erosion and necrosis. Contrast-enhanced CT scan can detect cavernous sinus thrombosis and can show enhancement of vessels. Magnetic resonance imaging (MRI) is an inherently multiplanar imaging

modality, which has excellent soft tissue contrast resolution and is more helpful in clearly delineating early vascular invasion and perineural and intracranial spread, especially using T2-weighted fat-suppressed and short-T1 inversion recovery (STIR) sequences. MRI permits detection of imaging signs, which are difficult to demonstrate on CT such as cavernous sinus involvement, vascular invasion, perineural spread, optic nerve infarction, and differentiation of cerebral parenchymal invasion from infarction with better visualization of periantral and infratemporal fossa extension, orbital soft tissue involvement, and skull base invasion [58]. A retrospective case–control study has shown that MRI was more sensitive than CT (85% vs 57%) for the diagnosis of acute fulminant invasive fungal sinusitis [59]. Contrast-enhanced MRI is considered the imaging modality of choice, as it can help delineate the necrotic tissue to guide the extent of resection [60].

Biopsy should be considered if mucormycosis is the potential diagnosis and definite diagnosis is ascertained by the demonstration of the characteristic non-septate or pauciseptate, irregularly branching ribbon-shaped hyphae in the tissue specimens (can even be demonstrated by microscopic examination of specimen in KOH [potassium hydroxide] wet mount preparation). Culture of specimens is recommended for genus and species recognition. Polymerase chain reaction (PCR) amplification and sequencing were first applied to better identify isolates that were grown from cultures of biopsies or bronchoalveolar lavage samples [61]. Matrix-assisted laser desorption ionization–time of flight (MALDI-TOF) mass spectrometry is a molecular technique used to identify Mucorales from cultures [62]. Internal transcribed spacer (ITS) sequencing has been proposed as a valuable target for resolution to genus and usually to the species level by the Clinical and Laboratory Standards Institute (CLSI) guidelines for fungal identification [63]. Recently, non-invasive PCR-based procedures have been used to detect Mucorales DNA in samples, such as plasma, serum or urine. These techniques can be performed in any patient; they help to anticipate the diagnosis of mucormycosis, distinguish between *Aspergillus* and Mucorales infections very early thereby improving patient outcome [64]; elevated serum galactomannan can help to differentiate invasive aspergillosis from mucormycosis [65].

Treatment

Mucormycosis is a medical as well as surgical emergency and requires rapid action. Empirical antifungal medication and surgical debridement should be considered early in the course of infection in potential cases of ROCM based on risk factors, clinical features and imaging findings. No guidelines are available for management of mucormycosis

in COVID-19 patients; the guidelines for mucormycosis are usually adopted with individualized modifications [61]. A tripartite approach is usually adopted consisting of reversal of the immunosuppressive state, administration of antifungal medication and extensive surgical debridement.

It is prudent to withdraw immunosuppressive medication in patients with COVID-19 and mucormycosis considering their devastating consequences. Other metabolic abnormalities that contribute to immunosuppressive state including hyperglycemia, acidosis, dyselectrolytemia and hypoxia should be corrected. Granulocyte colony-stimulating factor can be considered in case of leucopenia to boost the immune response.

Intravenous liposomal amphotericin B at a dose of 10 mg/kg/day is the first-line antifungal agent of choice for monotherapy of CNS mucormycosis, with full dose from day-1. In case of renal dysfunction, which is common in severe COVID-19 patients with multiple organ dysfunction syndrome (MODS), dose modification is not needed but the timing of administration of liposomal amphotericin B in relation to any form of renal replacement therapy should be decided based on nephrology opinion [39]. However, a dose of less than 5 mg/kg/day has only a marginal supporting evidence. In the absence of CNS involvement, amphotericin B lipid complex (5 mg/kg/day) can also be considered. Other antifungal medications include intravenous isavuconazole (3 × 200 mg on day 1–2, 1 × 200 mg per day from day 3), intravenous posaconazole (2 × 300 mg on day 1, 1 × 300 mg per day from day 2), and posaconazole oral suspension (4 × 200 mg per day), which can be considered in case of renal dysfunction as an alternative to liposomal amphotericin B, or as an add-on in progressive disease as part of salvage therapy. They can also be started in combination with liposomal amphotericin B in case of extensive disease, rapid progression, or poor general condition. Although effective, the use of amphotericin B deoxycholate is limited by its adverse effects and should only be considered when no other antifungals are available. Maintenance therapy with isavuconazole or posaconazole can be considered once the disease is stabilized. Treatment should be continued till complete reversal of immunosuppression and resolution of disease as suggested by imaging [61]. Availability of antifungal medication and affordability issues significantly affect the therapy in developing countries in addition to comorbidities like renal dysfunction.

As amphotericin cannot attain therapeutic concentrations in necrotic tissue, whenever possible, early extensive surgical debridement or resection should be performed in mucormycosis, which is the key for disease control and helps in histopathological and microbiological diagnosis [61]. Hyperbaric oxygen therapy is expected to improve hypoxia and acidosis, thereby restricting fungal multiplication; however, its role is yet to be established [66].

In a review of 929 patients with zygomycosis, 64% were treated with some form of antifungal chemotherapy with a survival rate of 62% (369 of 596 patients). The survival rates of patients treated with surgery alone was 57% and for those treated with a combination of surgery and antifungal chemotherapy 70%; survival rate was only 3% when no treatment was received [51].

Steps for prevention of mucormycosis in patients with COVID-19

- A detailed history regarding the medical comorbidities (DM, organ transplantation, malignancies) can help in fine-tuning the treatment and reduce the risk of opportunistic infections.
- Knowledge about patient's current medications (including immunosuppressants) is crucial for medical reconciliation and prevention of additional immunosuppression.
- Corticosteroids and other immunomodulators should be used judiciously with right timing at the evidence-based dose and for the recommended duration.
- Irrational use of antibiotics should be avoided.
- Strict monitoring of blood glucose levels in admitted as well as discharged patients and prompt correction are critical.
- Use of insulin is prudent in patients with DM admitted for treatment of COVID-19.
- There should be a constant vigil to detect risk factors such as DKA, acidosis, hypoxia, and leucopenia and necessary steps should be initiated immediately for their correction.
- Use of clean sterile water in humidifiers can reduce the risk of infection.

Conclusion

Mucormycosis is an angioinvasive fungal infection increasingly being reported in patients with COVID-19. Irrational use of immunosuppressants (corticosteroids in particular) and antibiotics, hyperglycemia, acidosis, hypoxia, iron disequilibrium and endothelial injury are some of the important risk factors for mucormycosis in the setting of COVID-19 pandemic. A high degree of suspicion is a must for early diagnosis and prompt treatment to reduce morbidity and mortality. Reversal of immunosuppressive state, correction of metabolic parameters, administration of antifungal medication and early aggressive surgical debridement are the recommended management strategies.

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