

# Coronavirus disease (COVID-19)-associated mucormycosis (CAM): The unholy triad of COVID-19, diabetes mellitus, and corticosteroid therapy

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## ABSTRACT

The whole world has battled with multiple waves of coronavirus disease 2019 (COVID-19) pandemic caused by severe acute respiratory syndrome coronavirus 2 virus. However, the second wave of COVID-19 had caused a worldwide havoc in terms of disease transmissibility, severity, and mortality. India has been among the worst hit countries during the second wave, which substantially overburdened and overwhelmed the Indian health care system. While secondary infections and co-infections among COVID-19 patients were increasingly being reported, COVID-19-associated mucormycosis (CAM) emerged as a new challenge particularly from India and became a matter of immediate concern. The most common causes attributed to the rise of CAM were undiagnosed/uncontrolled diabetes mellitus, excessive use of corticosteroids, and prolonged hospital stay, all of which create a perfect environment for mucormycosis infection to set in.

**Keywords:** Arcturus, diabetic ketoacidosis, invasive fungal infection, mucorales, omicron, variant of concern

## Background

While the whole world has battled with multiple waves of coronavirus disease 2019 (COVID-19) pandemic caused by severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2), lately, the second wave of COVID-19 had caused a worldwide havoc in terms of disease transmissibility, severity, and mortality. During the second and third waves, the emerging new variants of SARS-CoV-2, often referred to as variants under investigation (VUI) or variants of concern (VOC), have been

the major cause of concern. India has been among the worst hit countries during the second wave of COVID-19 (primarily driven by the 'delta' variant of SARS-CoV-2), which substantially overburdened and overwhelmed the Indian health care system. On May 6, 2021, India recorded 414,280 new cases, and on May 18, 2021, India recorded 4529 deaths and accounted for a maximum number of new cases and deaths due to COVID-19 in 24 hours<sup>[1]</sup> and by the third week of May 2021, India contributed to approximately 45% of new cases and 34% of the deaths, recorded globally.<sup>[2]</sup>

As India continued to gradually recover and attain stability over the existing situation, secondary infections and co-infections, particularly the invasive fungal infections (IFIs), were reported increasingly among COVID-19 patients.<sup>[3]</sup> While

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COVID-19-associated pulmonary aspergillosis, complicating the course of COVID-19, is a widely recognized IFI, another eminent threat in the form of COVID-19-associated mucormycosis (CAM) has emerged as a new challenge.<sup>[3,4]</sup>

## The Black Fungus

Mucormycosis, which was often referred to as 'black fungus'<sup>[5,6]</sup> in the Indian media reports during the second wave of COVID-19, is a rare but lethal mould infection, caused by saprophytic fungi of order Mucorales and family Mucoraceae.<sup>[7]</sup> The most common organisms involved are *Rhizopus*, *Mucor*, *Rhizomucor*, *Lichtheimia*, *Cunninghamella*, *Syncephalastrum*, *Apophysomyces*, and *Absidia species*.<sup>[6]</sup> The disease can locally infect the paranasal sinuses and later can spread to surrounding structures: inferiorly to palate, laterally into the cavernous sinus and the orbits, and cranially into the brain, resulting in rhino-orbito-cerebral mucormycosis (ROCM), the most common type of human mucormycosis, with pulmonary, gastrointestinal, cutaneous and disseminated being the other less commonly encountered forms.<sup>[8]</sup> Symptoms include headache, facial and/or retro-orbital pain, facial edema, chemosis, proptosis, ptosis, rhinorrhea, nasal blockade, intra-nasal/intra-oral black necrotic areas, epistaxis, and in more serious cases ophthalmic and cranial nerve involvement.<sup>[9]</sup>

First described by Paltauf in 1885, mucormycosis is the third most common opportunistic fungal infection after candidiasis and aspergillosis.<sup>[10]</sup> Black fungus, although actually a misnomer, is referred so due to the presence of characteristic black necrotic lesions on the affected areas (particularly nasal bridge or the hard palate), which can fulminate very quickly.<sup>[6]</sup> This rapidly progressing IFI usually affects individuals with an altered immune system more so among the diabetic patients with diabetic ketoacidosis (DKA) and is often referred to as the diabetes-defining illness and remains one of the most devastating complications in uncontrolled diabetics with mortality rates ranging between 40 and 80%.<sup>[7,11,12]</sup>

In comparison to the first wave of COVID-19, the incidence of mucormycosis had risen more rapidly during the second wave. By June 28, 2021, India had reported over 40,845 cases of mucormycosis, with 31,344 cases of rhino-cerebral in nature. Out of the total cases reported, 34,940 (85.5%) patients had COVID-19 infection, 26,187 (64.1%) had diabetes as co-morbidity, and 21,523 (52.7%) were on corticosteroid therapy.<sup>[13]</sup> Except for the states of Gujarat and Maharashtra, who had contributed to the maximum number of CAM cases, other states including Uttarakhand also showed a steady rise in the number of mucormycosis cases, which was eventually declared as an epidemic and a notifiable disease to the national health authorities.<sup>[14]</sup> Consequent to the surge in CAM cases and as per the directives from the Government of India, on May 9, 2021, the Indian Council of Medical Research (ICMR) released guidelines for the screening, diagnosis, and management of mucormycosis among COVID-19 patients.<sup>[15]</sup>

## The Association

The most common causes attributed to the rise of mucormycosis among COVID-19 patients were undiagnosed/uncontrolled diabetes mellitus (DM), excessive use of corticosteroids, and prolonged hospital stay, all of which create a perfect environment for mucormycosis infection to set in.<sup>[7]</sup> Hyperglycemia is associated with diminished polymorphonuclear leukocyte activity, impaired chemotaxis, and defective intra-cellular killing mechanisms.<sup>[16]</sup> Diabetic patients also have altered innate and cell-mediated immunity, cytokine secretion, and decreased natural killer cell activity,<sup>[16]</sup> which not only contributes to the severity of COVID-19 infection but also predisposes them to IFIs including mucormycosis. Except for the above, patients with DKA have free iron available in their serum, and through siderophores or iron permeases, it is taken up by the Mucorales, contributing further to their virulence,<sup>[16]</sup> and can aggravate the extent and severity of mucormycosis among them.<sup>[4]</sup> Moreover, all the aforementioned mechanisms are potentiated by corticosteroid therapy; in addition, corticosteroids themselves can cause steroid-induced hyperglycemia, impaired neutrophil migration, ingestion, and phagolysosome fusion, and thus, the extensive use of steroids in COVID-19 management may have amplified the risk of acquiring mucormycosis.<sup>[4,17]</sup>

Except for the aforementioned host-related factors associated with CAM, widespread use of broad-spectrum antibiotics, use of invasive ventilation, and the ubiquitous distribution of Mucorales in the environment (particularly in the hospital settings) have been reported to be the other confounding factors associated with CAM.<sup>[18]</sup> Broad-spectrum antibiotics interrupt the healthy sino-nasal microbiome, possibly enabling the asexual spore forms of Mucorales to infect the oral and nasal cavities through inhalation.<sup>[19]</sup> Among the immunocompromised individuals with COVID-19 infection, the diminished leucocyte activity fails to clear the infection and the spores develop into hyphal forms which proliferate and invade the vessel walls of the infected region, resulting in thrombosis, ischemia, and eventually necrosis.<sup>[8]</sup> Environmental factors including hot and humid climate (tropical/sub-tropical), predominance of some of the Mucorales species in soil, high Mucorales spore counts in the hospital and its vicinity, the unhygienic handling of the oxygen, and the inferior tubing and impure water source used in humidifiers have been documented to encourage the growth of Mucorales and provide a conducive environment for disease progression.<sup>[19,20]</sup>

## The Response

To ascertain the control over the situation, the government issued tailored guidelines, formulating special task forces, arranging dedicated wards for management of mucormycosis, and speedy procurement of the antifungal drugs (amphotericin B, posaconazole, isavuconazole) required for treatment. Although initially the shortage of amphotericin B was noticed in multiple states, timely measures implemented in terms of procurement,

optimal allocation, and ramping up the domestic production of amphotericin B had been instrumental. However, the government still needs to continuously monitor and analyze the situation, educate and disseminate information to the general public, and effectively and efficiently implement essential measures for preventing any further rise in the number of CAM cases. Such measures become more imperative in the view of ongoing COVID-19 pandemic, and although the third wave in India, primarily driven by the omicron variant, has passed, more recently, surge in COVID-19 cases has been noted and is being viewed as a possible fourth wave. According to the reports, the recent surge in COVID-19 cases is attributed to a new sub-variant 'Arcturus' (XBB.1.16), first identified from Maharashtra on January 11, 2023.<sup>[21,22]</sup> According to the WHO's weekly epidemiological update, published on May 4, 2023, XBB.1.16 variant was already reported from 40 countries.<sup>[23]</sup> Karyakarte *et al.* retrieved 2586 SARS-CoV-2 genomic sequences through GISAID (submitted from India between December 1, 2022 and April 8, 2023), conducted a phylogenetic analysis of the same, and reported XBB.1.16 to be the most predominant SARS-CoV-2 variant accounting for about 36% of the new COVID-19 cases.<sup>[24]</sup> Studies suggest that XBB.1.16 has a greater growth advantage in the human population compared to XBB.1 and XBB.1.5 and hence, XBB.1.16 may spread worldwide in near future.<sup>[25]</sup> Considering the same, the possibility of upsurge in CAM cases (as seen during the second wave) cannot be ignored.

To summarize, primary care physicians caring for critically ill COVID-19 patients must be aware of IFIs like mucormycosis that can not only complicate the course of COVID-19 but also deteriorate the patient outcome. A high degree of clinical suspicion is required for early diagnosis and ensures effective and efficient management of CAM. The information collated in this article will be helpful for primary care physicians, who are among the first line medical care givers, particularly in the rural and resource-constrained settings, and hence, they need to be well informed about any latest guidelines and associated complications pertaining to COVID-19. This will not only help to generate accurate and reliable data regarding COVID-19 but also help to tailor the prevention and mitigation strategies accordingly.

## Conclusion

India bears the dubious distinction of being both the diabetes and mucormycosis, 'capital' of the world. Although the incidence of mucormycosis in the western world is low (0.005 to 1.7 per million population), due to the high prevalence rate of DM (8.9%), the incidence in India (140 cases per million population) is quite high and India contributes to 40% of the global burden of this "rare mould" infection.<sup>[5]</sup> A high index of clinical suspicion, early clinical and/or laboratory diagnosis, and a coordinated multi-disciplinary approach can improve the patient outcome. Controlling underlying conditions like hyperglycemia, early treatment with liposomal amphotericin B, surgical intervention, and adjuvant therapy with caspofungin, deferasirox, statins, aspirin, and hyperbaric oxygen are essential

for successful management of mucormycosis cases among patients with COVID-19 infection.

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## Conflicts of interest

There are no conflicts of interest.

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