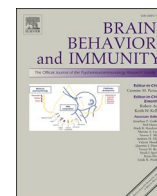




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Viewpoint

The mucormycosis epidemic within COVID-19 pandemic- lessons from India

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With the escalation of cases world-wide, a myriad of complications from Coronavirus disease (COVID-19) are being increasingly appreciated, including the vulnerability to secondary bacterial and fungal infections, which may occur in approximately 8% of hospitalised patients (Mehta and Pandey, 2020). COVID-19 causes an immunosuppressed state and increases risk of secondary infections like mucormycosis. There was an unprecedented rise in mucormycosis cases, colloquially called the ‘black fungus’, amidst a massive second-wave of Covid-19 pandemic in India (Singh et al., 2021).

Mucor, a fungus present ubiquitously in the environment, can cause a potentially fatal opportunistic infection, leading to invasion of blood vessels by fungal hyphae, causing infarction and necrosis of a variety of end-organ host tissues (Werthman-Ehrenreich, 2021). Rhino-orbital infection of mucorales species of fungus (Fig. 1A,1B), especially with extension to the brain (Fig. 1C, 1D) portends a poor prognosis with a mortality rate reaching 50%, even with appropriate treatment (Werthman-Ehrenreich, 2021). Mucormycosis is known to affect immunocompromised patients especially those with diabetes mellitus, prolonged corticosteroid use, solid organ transplant recipients, neutropenia and hematological malignancies (Mehta and Pandey, 2020; Mekonnen et al., 2021). Even in the pre-Covid-19 era, India had the highest burden of mucormycosis globally (Sen et al., 2021). However, the sudden spike of mucormycosis during the second wave of Covid-19 in India wreaked havoc due to its poorly understood reasons, large numbers, inadequate supply of essential medicines, poor healthcare infrastructure and further increased the mortality. We postulate that the synergistic interaction of several substrates – host, pathogen and environment – acted in concert and predisposed to this phenomenon (Fig. 2).

Impaired host defence- SARS-CoV-2 infection impairs cell-mediated immunity and decreases CD4+ and CD8+ cell counts, predisposing fungal infections (Singh et al., 2021). In India, it occurred on the

backdrop of a high prevalence of uncontrolled diabetes mellitus, an independent risk for mucormycosis (Singh et al., 2021). The widespread and injudicious use of corticosteroids, broad-spectrum antibiotics, immunomodulatory treatments (e.g. tocilizumab), and invasive mechanical ventilation might have caused further immune dysregulation among Covid-19 patients (Singh et al., 2021; Selarka et al., 2021).

Increased virulence of pathogen- During the course of Covid-19 illness, many factors could have facilitated in creating an ideal milieu for Mucorales fungus to thrive and propagate, which include immune dysregulation (suppressed cell-mediated immunity), steroid-induced hyperglycaemia, acidotic environment (metabolic acidosis, diabetic ketoacidosis), hypoxia (pneumonia), hyper-ferritinemia and complement-mediated thrombotic microangiopathy (Singh et al., 2021; Selarka et al., 2021). Furthermore, the empirical supplementation of multivitamins and zinc, believed to combat Covid-19 virus, might have enhanced the pathogenic virulence of Mucorales (Wilson et al., 2012).

Environment- As healthcare systems across India became inundated with Covid-19, acute shortage of medical oxygen led to desperate use of industrial oxygen as an alternative. While medical oxygen is highly purified with cylinders rigorously disinfected, the same may not be ensured for industrial oxygen and the impurities could have contained rust (rich in iron- and a facilitator of fungal growth) (World Health Organization, 2020). Additionally, the administration of high-flow oxygen, especially over a prolonged duration and with makeshift oxygen delivery systems, could not have used the required sterile water for humidification, and increased the risk of fungal infections. Furthermore, damaged lining of nostrils due to aggressive suctioning of secretions provided a readymade template for fungal growth. Finally, unsanitary re-use of face-masks, especially during the prevailing hot and humid weather were further responsible for exacerbating this risk.

Covid-19 pandemic is not over yet. Increasing number of countries,

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<https://doi.org/10.1016/j.bbi.2021.08.005>

Received 27 July 2021; Received in revised form 3 August 2021; Accepted 3 August 2021

Available online 8 August 2021

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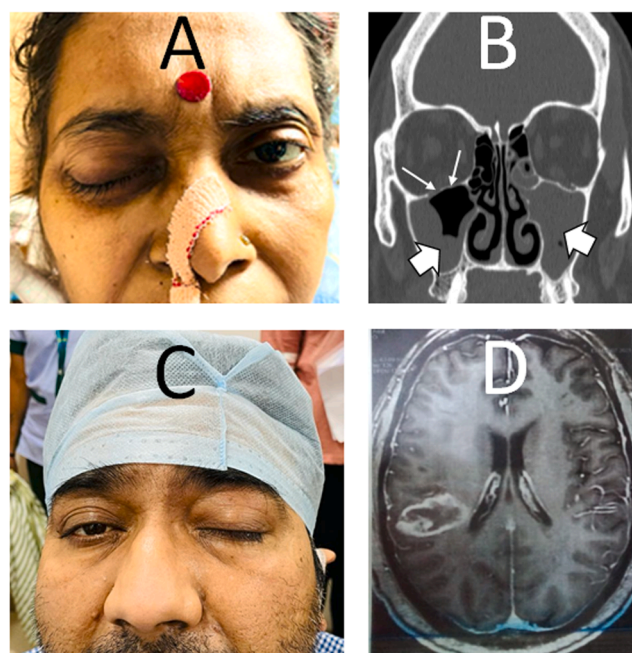


Fig. 1. Examples of Rhino-orbital and Rhino-orbital-cerebral mucormycosis among Covid-19 patients. A 71-years old women suffered from blackish discharge from nostrils on day 12 of Covid-19 infection followed by progressive pain in the right eye, diminished vision and complete ophthalmoplegia (1A). Panel B shows opacification of both maxillary sinuses (thick arrows) with erosion of the orbital plate (thin arrows). Panel C shows a 49 years old man who developed blocked nostrils and left ophthalmoplegia after 13 days of the diagnosis of Covid-19. On day 15, he developed left hemiparesis due to an abscess in the right frontotemporal region (seen on contrast magnetic resonance imaging in panel D). Diagnosis of mucormycosis was confirmed in both patients by direct microscopy of naso-endoscopic specimens with potassium hydroxide mount and microbiological/histological confirmation. Both patients were treated with intravenous amphotericin B for 3 weeks and recovered satisfactorily. However, their vision in the affected eye could not be restored.

especially with poorer hygienic conditions and inadequate resources are witnessing rising number of cases, overwhelming their healthcare services, creating severe shortages of oxygen and essential medications. Mucormycosis epidemic may surface in these countries, multiplying the disease burden and mortality. We feel an urgent need to identify various components responsible for the dreaded mucormycosis epidemic among Covid-19 patients. Rapid and mass vaccination of the general population hold the key for winning the ongoing battle against the current pandemic. Aggressive actions to break the chain of propagation of opportunistic fungal infections would be required to culminate the mucormycosis storm, especially in high-risk populations to avert additional morbidity and mortality.

Funding source

None.

Author contributions

JJYO- literature review and first draft
 ACYC- Coceptualization and critical review
 AKS- data collection, critical review
 SS- data collection, critical review
 VKS- conceptualization, critical review and final approval

Declaration of Competing Interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

Acknowledgement

We are thankful to both patients in Fig. 1 for providing written consent for reproduction of their faces and imaging details.

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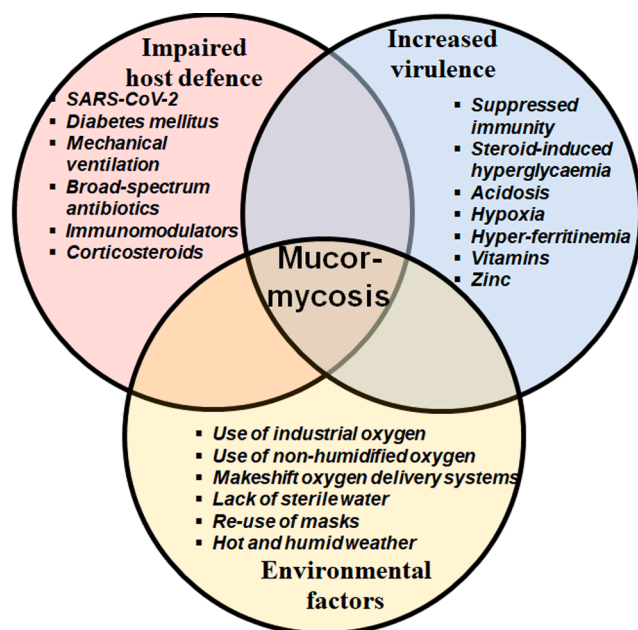


Fig. 2. Potential predisposing factors acting in synergy for the increased risk of mucormycosis in the context of Covid-19 pandemic.