


# “Black fungus”: a perspective on the coronavirus disease 2019 (COVID-19)-associated rhino-orbital mucormycosis epidemic in India

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## KEYWORDS

COVID-19, fungal sinusitis, immunodeficiency, paranasal sinus diseases, rhinosinusitis, steroid therapy, therapeutics

Multiple reports from India have documented a precipitate rise in coronavirus disease 2019 (COVID-19)-associated rhino-orbital-cerebral mucormycosis (CAROM) since March 2020.<sup>1,2</sup> The overall risk of developing CAROM in the backdrop of COVID-19 was recently estimated to be approximately 1 in 400.<sup>2</sup> CAROM in India is typically being noted 2 to 4 weeks from the onset of COVID-19. The cause of the unexpectedly high incidence of CAROM in India has resulted in widespread speculation. CAROM has been labeled by the press and public as “black fungus” based on the black color of necrotic tissue. Notably, the causative fungal spores or mycelia are not black. Fungi that cause CAROM are ubiquitous in our environment and may be part of our normal sinonasal flora. Opportunistic fungal infections such as CAROM only occur when the host develops uncontrolled hyperglycemia or significant immunosuppression.

COVID-19 can cause immunosuppression through broad alterations of the innate immune system and CD4+ and CD8+ T cell lymphopenia.<sup>3</sup> In reported series from India, CAROM is usually associated with the triad of COVID-19-associated immune suppression/dysregulation, uncontrolled hyperglycemia, and use of corticosteroids and other immunosuppressive medications. The unfortunate melding of these circumstances increases host susceptibility to CAROM and other opportunistic infections.<sup>1–3</sup> This triad in itself, however, may insufficiently explain the entire story of CAROM in India,

and further scientific enquiry is ongoing. Unverified and speculative reports in the lay press have caused alarm by ascribing causation of CAROM to the use of industrial oxygen and unsterile water in oxygen humidifiers. Given that the majority of patients with CAROM have had mild or moderate COVID-19 and have never required oxygen, such speculation may be misplaced and indeed mischievous. Nevertheless, there are some unique population and cultural factors relevant to the Indian subcontinent that may have facilitated this catastrophic rise in CAROM. This letter shares our perspectives on CAROM in India.

The pre-epidemic incidence of mucormycosis in India has been previously estimated to be significantly higher than global incidence rates.<sup>4</sup> The temperate weather conditions of the recent months in India may have contributed to an infection known to have seasonal predilection.<sup>3,4</sup> Diabetes mellitus is widely prevalent in the adult Indian population and unfortunately may sometimes be poorly controlled or diagnosed. Additionally, limitations to accessing medical care in the current epidemic has likely exacerbated the population prevalence of poorly controlled hyperglycemia/diabetes. The prevalence of cardiac and chronic obstructive pulmonary disease is also higher in many urban populations in India; these conditions may further contribute to susceptibility and mortality to opportunistic infections.<sup>4</sup>

Evidence-based guidelines and protocols have been developed by the Indian Council of Medical Research

in concert with the All India Institute of Medical Sciences.<sup>5</sup> However, the high mortality from the current wave of COVID-19 may have led to panic-induced overuse of multiple drugs at higher doses and durations than recommended. Paradoxically, the use of these drugs as single agents or in combination therapy facilitates conditions for genesis of opportunistic infections such as CAROM.<sup>3,6</sup> Glucocorticoids may precipitate the onset of diabetes, inhibit cellular immune responses, and cause immunosuppression.<sup>4</sup> Broad-spectrum antibiotics and use of “prophylactic” antifungals disrupt the healthy sinonasal microbiome, potentially facilitating opportunistic infections. Macrolide antibiotics such as azithromycin also inhibit interleukin 6 (IL-6), a cytokine that is critical to the normal antimicrobial immune response.<sup>6</sup> Tocilizumab, an IL-6 inhibitor, is recommended for use in the postinfection cytokine storm; when used otherwise, this drug can dampen normal immune responses.<sup>6</sup>

Indian healthcare also has yet not been able to curtail over-the-counter sale of antibiotics, systemic corticosteroids, and other potentially dangerous medications to customers without valid prescriptions. A vast section of the Indian population is therefore highly accustomed to self-medication prior to seeking care with a physician. Social media interactions and groups have tended to exacerbate this behavior with news and views on novel and untested paradigms.

Lay patients, semi-informed and armed with information from social media and the internet, untutored to the nuances of clinical judgment and judicious use of drugs, have unfortunately been accessing self-treatment, using drugs inappropriately, or prolonging treatments beyond medically-prescribed durations.

The CAROM crisis can be effectively controlled through continued education of colleagues and patients on the advantages of evidence-based, nuanced strategies that leverage thoughtful and discriminate usage of drugs. The public must be cautious in accessing social-media and panic-driven self-treatments; these may cause hyperglycemia and immunosuppression, allowing CAROM to take root and counterproductively increase morbidity and

mortality. Through this letter, we also salute our colleagues in India who are courageously battling the current calamity with resources far more limited than in the United States, and circumstances much more challenging.

## CONFLICT OF INTEREST

None provided.

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**How to cite this article:** Thakar A, Lal D. “Black fungus”: a perspective on the coronavirus disease 2019 (COVID-19)-associated rhino-orbital mucormycosis epidemic in India. *Int Forum Allergy Rhinol.* 2021;11:1278–1279. <https://doi.org/10.1002/alr.22855>