



COMMENTARY

COVID-19-associated mucormycosis: an epidemic within a pandemic

R. Sarda , S. Swain, A. Ray  and Naveet Wig

From the Department of Medicine, All India Institute of Medical Sciences, 3rd Floor Teaching Block, Ansari Nagar, New Delhi 110029, India

Address correspondence to Dr A. Ray, Department of Medicine, All India Institute of Medical Sciences, Room no: 3070A, 3rd Floor Teaching Block, Ansari Nagar, New Delhi 110029, India. email: doctoranimeshray@gmail.com

India continues to battle the second wave of COVID-19 and has recently reported the highest number of cases ever in a single day from a country. As severe COVID-19 continues to claim thousands of lives in this country, there has also been a recent spate of COVID-19-associated mucormycosis (CAM) cases which have garnered attention globally. More than 14 000 cases of CAM have been reported from all over India with many states resorting to declaration of an epidemic as well as making it a notifiable disease.¹ We wish to elaborate on the evolving situation of CAM in India with special attention to the association of mucormycosis with COVID-19, the pathophysiological basis for CAM, likely reasons for preponderance of CAM in India as well as the core management issues.

The association of COVID-19 with recent increase in incidence of rhino-orbital mucormycosis has been linked to a number of possible etiological factors. SARS-CoV-2 may lead to impaired cell-mediated immunity, lymphopenia and associated reduction in CD4⁺ and CD8⁺ cell population.² Steroid-induced hyperglycemia and immunosuppression, often against a background of uncontrolled diabetes mellitus (with or without diabetic ketoacidosis), is considered as a *sine qua non*. Further endothelial damage, endotheliitis and thrombosis due to interplay of COVID-19 and diabetes can also predispose to fungal infection.³

Mucor is a saprophyte widely found in the environment and it can also be found as a commensal in the nasal cavity. Several pathophysiological mechanisms have been proposed to explain the loco-regional growth and dissemination of mucormycosis.⁴ Acidotic milieu in the presence of ketones along with

hyperglycemia; glycosylation of ferritin (acute phase reactant which is increased in COVID-19) leading to generation of free iron, are some of the factors which facilitates the growth of *Mucor*. Also, the combination of hyperglycemia, low pH, high iron and acidosis decreases the phagocytic activity of leucocytes and enhances the expression of GRP-78 (glucose receptor protein-78) of endothelial cells and fungal ligand spore coating homologue protein (CoH). This unique interaction between CoH and GRP-78 can lead to enhanced *Mucor*-induced angiogenesis and necrosis.

The increased incidence of CAM in India, as compared to other countries, has also been deliberated on and few reasons can be attributed to. The sudden surge in COVID-19 cases during second Indian wave led to collapse of already strained health-care system with dearth of hospital beds and perilously low oxygen supply. As a result, patients with mild to severe COVID were compelled to be managed at home (with steroids and other drugs) which could have led to suboptimal monitoring especially of blood glucose levels and early signs of mucormycosis.⁵ From pre-COVID era, prevalence of mucormycosis is known to be at least 70 times higher in India as compared to other countries, highlighting a strong background presence.⁶ Environmental preponderance of certain species of *Mucorales* like *Apophysomyces*, in Indian soil can be a possible factor for the same.⁷ India is home to the second largest pool of diabetics (prevalence ~8.9%) worldwide, with up to 42% of them being undiagnosed.⁸ Various other theories are mulled over like prolonged use of unhygienic masks, new construction sites, overcrowding, repeated traumatic sampling; however further

Received: 5 June 2021; Revised (in revised form): 6 June 2021

© The Author(s) 2021. Published by Oxford University Press on behalf of the Association of Physicians. All rights reserved.

For permissions, please email: journals.permissions@oup.com

research needs to be done before their roles could be established. Interaction of all these factors; suitable agent, host and environment; has promoted the establishment of the perfect 'epidemiological triad' leading to an explosive increase in the CAM cases in India.

The implications of managing CAM are multifold. The disease itself has a very high mortality with a range of 28–52% in different studies.⁹ It entails the use of costly and toxic antifungals like amphotericin B and posaconazole which have to be administered for a prolonged duration adding significantly to the economic burden. The requirement of risky and potentially disfiguring surgical interventions adds to the mortality and morbidity of this disease. The interventions, which requires considerable expertise and interdisciplinary co-ordination (ophthalmology, otorhinolaryngology, neurosurgery, microbiology, internal medicine, infectious diseases, etc.), can only be conducted at advanced centers and becomes even more challenging against the backdrop of the pandemic.¹⁰

The way forward for tackling this menace is to rigorously strengthen the country's healthcare system, judicious use of steroids, close monitoring of glycemic status in patients of COVID-19, adhering to guidelines for using hygienic masks, regular monitoring of at-risk COVID-19 patients for timely detection of mucormycosis, ramping up of anti-fungal drug supply and inter-departmental collaboration for appropriate management.

While several aspects of this intriguing disease have come to the fore during this pandemic, the most important preventable factor to address the 'disease triangle' of CAM seems to be the judicious and supervised use of steroids in COVID-19 with protocolized monitoring of blood glucose. While future research will continue to throw light on the different nuances of this disease, it is important that we appreciate the danger posed by this deadly infection and course-correct timely.

Conflict of interest. None declared.

References

1. Singh P. Black fungus: Here is a list of states with highest number of mucormycosis cases [Internet]. Hindustan Times. 2021. <https://www.hindustantimes.com/india-news/black-fungus-states-with-highest-number-of-mucormycosis-cases-101621559394002.html> (5 June 2021, date last accessed).
2. Tay MZ, Poh CM, Rénia L, MacAry PA, Ng LFP. The trinity of COVID-19: immunity, inflammation and intervention. *Nat Rev Immunol* 2020; **20**:363–12.
3. Jin Y, Yang JW, Chen H, Zhang S, Duan W. Endothelial activation and dysfunction in COVID-19: from basic mechanisms to potential therapeutic approaches. *Signal Transduct Target Ther* 2020; **5**:1–13.
4. Baldin C, Ibrahim AS. Molecular mechanisms of mucormycosis—the bitter and the sweet. *PLoS Pathog* 2017; **13**:e1006408.
5. Ray A, Goel A, Wig N. Corticosteroids for treating mild COVID-19: opening the floodgates of therapeutic misadventure. *QJM* 2021.
6. Prakash H, Chakrabarti A. Global epidemiology of mucormycosis. *J Fungi* 2019; **5**:26.
7. Prakash H, Ghosh AK, Rudramurthy SM, Paul RA, Gupta S, Negi V, et al. The environmental source of emerging *Apophysomyces variabilis* infection in India. *Med Mycol* 2016; **54**:567–75.
8. Anjana RM, Deepa M, Pradeepa R, Mahanta J, Narain K, Das HK, et al. Prevalence of diabetes and prediabetes in 15 states of India: results from the ICMR–INDIAB population-based cross-sectional study. *Lancet Diabetes Endocrinol* 2017; **5**: 585–96.
9. Prakash H, Chakrabarti A. Epidemiology of mucormycosis in India. *Microorganisms* 2021; **9**:523.
10. Huda F, Kumar P, Singh SK, Agrawal S, Basu S. Covid-19 and surgery: challenging issues in the face of new normal—a narrative review. *Ann Med Surg* 2020; **60**:162–7.