



Since January 2020 Elsevier has created a COVID-19 resource centre with free information in English and Mandarin on the novel coronavirus COVID-19. The COVID-19 resource centre is hosted on Elsevier Connect, the company's public news and information website.

Elsevier hereby grants permission to make all its COVID-19-related research that is available on the COVID-19 resource centre - including this research content - immediately available in PubMed Central and other publicly funded repositories, such as the WHO COVID database with rights for unrestricted research re-use and analyses in any form or by any means with acknowledgement of the original source. These permissions are granted for free by Elsevier for as long as the COVID-19 resource centre remains active.

## Letter to the Editor

### Pathogenesis of COVID-19-associated mucormycosis (CAM) in India: probing the triggering factors

Sir,

We read with great interest the reply letter ‘Additional insights on COVID-associated mucormycosis (CAM)’ that raises concerns about diverse factors that have contributed to the sudden surge in mucormycosis during the second wave of the COVID-19 pandemic.<sup>1</sup>

The authors have expressed their reservations about the scientific evidence supporting the association between mucormycosis and COVID-19 infections produced by the B.1.617.2 (Delta) strain.<sup>1</sup> Our original paper, however, sought to explore and raise awareness of the potential multifactorial risks of CAM during the Delta variant-predominant second wave in India, rather than to establish a simple viral-driven causal association.<sup>2</sup>

Conceptually, the relation between mucormycosis and the Delta variant can be explained by the fact that the sudden emergence of CAM during the second wave and the overwhelming majority of these mucormycosis cases have mainly occurred in the unvaccinated population. Therefore it is possible that vaccination prevented or reduced the severity of the adverse effects that cause mucormycosis. Furthermore, the majority of asymptomatic and untreated individuals with the Delta variant could represent resistant subgroups that had no CAM due to the lack of noticeable and evident deleterious effects on immune regulation or metabolic function. Given the huge research challenges and questions posed as the pandemic unfolded, the scientific groundwork that supported treatment and preventive efforts still remains an area of open debate.

While other countries are also reporting CAM cases, the number of cases in India is remarkably higher in comparison.<sup>3</sup> This was speculated to have been based on specific factors such as geographical distribution, genetic susceptibility, mucor organisms, and other native factors. Interestingly, all the above-mentioned factors, including high-dose steroid

therapy, were present even in the first wave, but without any sudden surge in cases.

This fact proves that some ‘uncommon factors’ (as opposed to specific factors), exclusive to the second wave, may have contributed to the pathogenesis of CAM. Our study noted that the uncommon factors were mostly the B.1.617.2 (Delta) variant and shortages in oxygen supply, both of which we have previously described.<sup>4</sup> This might also explain why other nations reported fewer CAM patients, maybe due to the absence of one or more of the specific components.

There is considerable debate concerning the role of steam inhalation and reuse of cloth (or surgical) masks in the aetiology of CAM. Their roles are over-rated since they have been common factors in both waves of COVID-19. We found no evidence to support their role in the existing literature, including the results of our study, as those patients did not have a history of prolonged or excessive steam inhalation.

Reuse of cloth masks was employed even during the first wave and continued after the second wave, although it did not result in a surge of CAM. Many individuals are exposed to microscopic fungal spores every day, so it is virtually impossible to avoid encountering mucormycetes completely.<sup>5</sup> Thus, instead of looking for the root cause and source, it is crucial to learn how the body becomes susceptible to the mucormycetes.

It appears that the triad of specific factors, common factors, and uncommon variables, such as the Delta variant and oxygen crisis, may have played a key role in the pathogenesis of CAM. The CAM triad may be helpful in formulating management strategies across different levels, hence it merits further study.

#### Ethics statement/confirmation of patients' permission

N/A.

## Declaration of competing interest

We have no conflicts of interest.

## References

1. Panta P. Additional insights on COVID-associated mucormycosis. *Br J Oral Maxillofac Surg* 2021. doi: 10.1016/j.bjoms.2021.09.020. Online ahead of print.
2. Rao VU, Arakeri G, Madikeri G, et al. COVID-19-associated mucormycosis (CAM) in India: a formidable challenge. *Br J Oral Maxillofac Surg* 2021;59:1095–1098.
3. Arakeri G, Rao VU, Mendes RA, et al. COVID-associated mucormycosis (CAM): is the 59 Delta variant a cause? *Br J Oral Maxillofac Surg* 2021. In press. Available from URL: <https://doi.org/10.1016/j.bjoms.2021.08.009> (last accessed 11 February 2022).
4. Rao VU, Arakeri G, Kaler AK, et al. Mucormycosis in COVID-19 2nd wave: hypoxia as key trigger and the biological impact of health policies. Available from URL: <https://www.bmj.com/content/373/bmj.n1238/r1-1> (last accessed 11 February 2022). Rapid response to: Covid 19: India sees record deaths as “black fungus” spreads fear. *BMJ* 2021; 373:n1238.
5. Fungal diseases: where mucormycosis comes from. Centers for Disease Control and Prevention. 14 January 2021. Available from URL: <https://www.cdc.gov/fungal/diseases/mucormycosis/causes.html> (last accessed 11 February 2022).

Gururaj Arakeri \*

*Department of Head and Neck Oncology, Centre for Academic Research, HCG Cancer Center, Bengaluru, Karnataka, India*

*Department of Oral and Maxillofacial Surgery, Navodaya Dental College and Hospital, Raichur, Karnataka, India*

\* Corresponding author at: Department of Head and Neck Oncology, Centre for Academic Research, HCG Cancer Hospital, Bengaluru, Karnataka, India.  
E-mail addresses: [gururaj.arakeri@gmail.com](mailto:gururaj.arakeri@gmail.com), [drgururaj.a@hcgel.com](mailto:drgururaj.a@hcgel.com)

Shreyas Patil

*Department of Medicine, RajaRajeswari Medical College and Hospital, Bengaluru, Karnataka, India*

Vishal Rao US

*Department of Head and Neck Oncology, Centre for Academic Research, HCG Cancer Center, Bengaluru, Karnataka, India*

Rui Amaral Mendes

*Department of Oral and Maxillofacial Medicine and Diagnostic Sciences, Case Western Reserve University, Cleveland, Ohio, United States*

*CINTESIS - Center for Health Technology and Services Research, Porto, Portugal*

Rachel S Oeppen

*Department of Clinical Radiology, University Hospital Southampton, SO16 6YD, United Kingdom*

Peter A. Brennan

*Department of Oral and Maxillofacial Surgery, Queen Alexandra Hospital, Portsmouth, United Kingdom*

Received 29 October 2021  
accepted 30 October 2021

Available online 15 November 2021