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Letter to the Editor

COVID-associated mucormycosis (CAM): is the Delta variant a cause?

Sir,

We read the response letter[1] to our recent paper on COVID-associated mucormycosis (CAM)[2] with great interest.

According to the letter, we have attributed the CAM surge to the Delta variant (B.1.617.2). However, our study does not imply so. Rather than a straightforward causal relationship, our study sought to address and discuss risk factors of CAM during the Delta variant-led second surge in India. We sincerely request the authors to revisit the discussion section of our work which addresses potential multidimensional risk factors.

However, our study underlined that the vast majority of mucormycosis cases are that of unvaccinated people and it is possible that the vaccination has prevented or decreased the severity of adverse effects causing immune dysregulation and mucormycosis.

Further, there is a possibility that the Delta virus adversely affects the pancreas,[3] thereby contributing to intense hyperglycaemia and in creating a favourable environment for the onset of mucormycosis. As much as hyperglycaemia and steroid usage need to be considered as triggering factors, one must, indeed, consider that these two variables were already present even in the first wave, although no similar outbreak of mucormycosis occurred at that time. In fact, in India, the routine use of high-dose glucocorticoids for cancer patients has never resulted in a mucormycosis epidemic. Furthermore, our study also involved home isolated COVID-19 patients who only took multivitamins and were not administered steroids or oxygen.

Although industrial oxygen may also be regarded as a contributing factor, its causality has not been conclusively demonstrated. Actually, it is not known why only some COVID-19 patients were infected and why cases were reported even after cessation of its use. Besides, there are many patients with CAM for whom external oxygen has never been necessary for treatment of COVID-19.

Remarkably, the mucormycosis epidemic in India was followed by an oxygen crisis, and many patients suffered with protracted subtle hypoxia throughout recovery, and many patients with minor symptoms were treated solely by home isolation without any oxygen. Hypoxia stimulates the endocytosis mechanism in some mucorales species, enabling the fungus metabolism to shift from carbohydrates to fatty acids, supplying fungi with extracellular lipids during infection.[4] It is possible that the combination of severe hyperglycaemia and prolonged hypoxia may have created the perfect conditions leading to a fast increase in the incidence of mucormycosis.

Finally, the fact that other regions of the world with Delta virus do not have an outbreak mucormycosis may be related to environmental, geographic, and genetic factors (indicated by the high pre-pandemic frequency in India) that may have predisposed immunologically dysregulated individuals to mucormycosis. However, there have been cases reported in Brazil, Chile, Honduras, Mexico, Paraguay, the United States, Uruguay, Italy, and the United Kingdom.[5] In fact, the Pan American Health Organization/World Health Organization (PAHO/WHO) has advised Member States in the United States to strengthen health services to prevent CAM-related morbidity and mortality.[5]

Overall, CAM appears to be a multifaceted issue which might have resulted in immunological dysregulation and therefore predisposed individuals to mucormycosis. Until more definite data are available, prudent administration of steroids, avoidance of long-term hypoxia, and management of blood glucose levels remain key preventive factors.

Ethics statement/confirmation of patients' permission

Not applicable.

Conflict of interest

We have no conflicts of interest.

References

1. Panta P, Stone N. COVID-associated mucormycosis (CAM) in India is a multidimensional problem. *Br J Oral Maxillofac Surg* 2021. https://doi.org/10.1016/j.bjoms.2021.08.008, S0266-4356(21)00334-X (online ahead of print).
2. Rao V, 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. Thapar K. Experts see link between B.1.617.2 and black fungus, want blood sugar monitored like oxygen. *The Wire*. Available from URL: https://thewire.in/health/watch-karan-thapar-black-fungus-covid-variant-blood-sugar-oxygen-mucormycosis (last accessed 30 December 2021).

https://doi.org/10.1016/j.bjoms.2021.08.009
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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. (Rapid Response). *BMJ* 2021;**373**:n1238.
5. Pan American Health Organization/World Health Organization. *Epidemiological Alert: COVID-19 associated mucormycosis*. 11 June 2021, Washington, DC: PAHO/WHO; 2021. Available from URL: https://reliefweb.int/sites/reliefweb.int/files/resources/2021-JUN-11-phe_Epi_Alert_Mucomycosis_COVID-19_Final_F.pdf (last accessed on 30 December 2021).

Gururaj Arakeri [a,b,*]
Vishal Rao US [a]
Rui Amaral Mendes [c,d]
Rachel S. Oeppen [e]
Peter A. Brennan [f]

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

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

[c] *Department of Oral and Maxillofacial Medicine and Diagnostic Sciences, Case Western Reserve University, Cleveland, OH, United States*

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

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

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

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

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