Neurological manifestations of rhino-oculo-cerebral mucormycosis in the COVID-19 era

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In India, the peak of SARS-CoV-2 infections in May 2021 was paralleled by an outbreak of rhino-oculo-cerebral mucormycosis (ROCM) — a fungal infection affecting the nose, eyes and brain. This outbreak provided a unique opportunity to study the neurological manifestations of ROCM and to investigate new treatments for the condition.

> “Most cases of ROCM are sporadic, but outbreaks can occur, especially in the setting of natural disasters”

Rhino-oculo-cerebral mucormycosis (ROCM) is a rare disorder in which the olfactory system and brain become infected with aerosolized spores from the *Mucorales* genus of fungi, which includes *Rhizopus*, *Apophysomyces*, *Mucor*, *Cunninghamella* and *Lichtheimia*. The spores first become established in the nasal cavity, leading to necrosis and, hence, local symptoms in the form of nasal stuffiness and discharge, which can contain blood. From here, the mucor fungus, which is highly angioinvasive, spreads sequentially to the maxillary and ethmoidal sinuses, the orbits, the cavernous sinuses, the meninges and, finally, the brain[1]. In addition, the skin overlying the sinuses and the soft tissues of the infratemporal fossae can be involved. ROCM is typically managed by multidisciplinary teams comprising otolaryngologists, ophthalmologists, endocrinologists, infectious disease specialists and maxillofacial surgeons, although neurologists might be called on to assess patients with this condition.

Risk factors for ROCM include diabetes mellitus (particularly if uncontrolled or in the diabetic ketoacidosis state), haematological malignancies, bone marrow or solid organ transplantation, iron overload states and immunosuppression[2]. Overall, mucormycosis is rare: a laboratory-based population survey in 1992–1993 estimated a prevalence of two cases per million individuals in California, USA[3], although the global incidence might subsequently have increased owing to rising numbers of transplantation procedures. The burden in India is particularly high, and is estimated to be 70 times greater than the expected global prevalence[4].

Most cases of ROCM are sporadic, but outbreaks can occur, especially in the setting of natural disasters. One of the largest outbreaks to date occurred in India in immediate temporal proximity to the second epidemic wave of COVID-19 — the clinical syndrome resulting from SARS-CoV-2 infection[5]. As SARS-CoV-2 infections hit a peak in the first week of May 2021, a slew of ROCM cases emerged across the country, and the Government of India responded by declaring mucormycosis a notifiable disease[6]. At the same time, India was experiencing a severe shortage of amphotericin B, the core ingredient in the therapeutic armamentarium against ROCM[6], creating the additional challenge of developing and implementing treatment protocols without ready access to this drug. Besides India, COVID-19-associated ROCM was reported, albeit anecdotally, in several other countries, including the USA, Iran and Brazil[7].

The rise, peak and fall in ROCM cases that closely followed the COVID-19 trend was intriguing and constituted a sufficient premise to propose a causal association between the two conditions, although the underlying mechanisms remain open to question. Interestingly, in one large multicentre study, 87% of individuals with COVID-19-associated ROCM had used corticosteroids as a standard regimen to treat the viral infection[8]. In addition, 78% of cases were associated with diabetes mellitus, which was usually uncontrolled and presented with diabetic ketoacidosis in 15% of cases[8]. Corticosteroid administration in the context of COVID-19 could potentially render patients susceptible to ROCM through corticosteroid-mediated hyperglycaemia or via other mechanisms such as immunosuppression. Elucidation of the precise mechanistic relationship between corticosteroid use, diabetes and COVID-19-associated ROCM will be crucial, given the already well-established link between diabetes mellitus and ROCM, especially in India[2].

ROCM can occur during active SARS-CoV-2 infection but typically follows subsidence of infection by 1–3 weeks[8]. Some individuals who present with ROCM are found to be coincidentally positive for SARS-CoV-2 by RT-PCR, and others do not report SARS-CoV-2 infection but are antibody positive, indicating prior exposure[8].

In the past, reports of neurological manifestations of ROCM have been scarce. The neurological manifestations of COVID-19-associated ROCM are not

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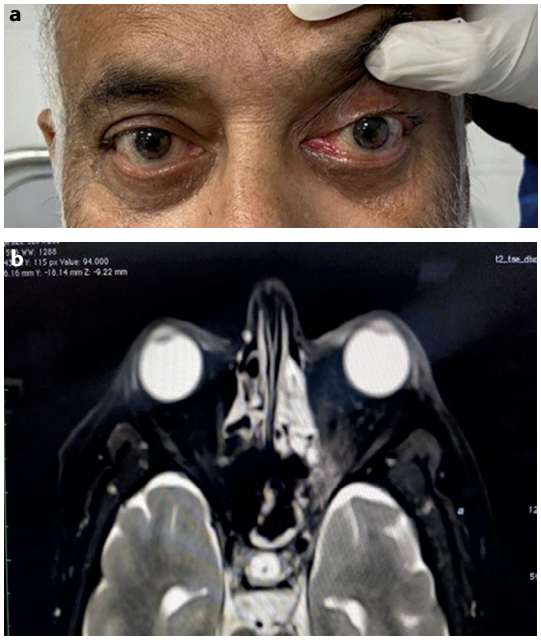

Fig. 1 | **Neurological manifestations of COVID-19-associated rhino-oculo-cerebral mucormycosis.** **a** | Proptosis of the left eye directed outwards, hinting towards ethmoidal sinusitis. **b** | Axial T2-weighted MRI scan of the same patient, showing ethmoidal sinusitis pushing the left eye outwards.

substantially different from those observed in the pre-SARS-CoV-2 era, so the COVID-19-associated ROCM outbreak provides an excellent opportunity to study these manifestations in more detail. The fungus can access the brain via the orbit, superior orbital fissure and cavernous sinus route; through the maxillary and mandibular nerves to Meckel's cave; or through the sphenoid sinus via the clivus. The clinical manifestations represent sequential and rapid involvement of these structures.

Orbital involvement in ROCM is common and results from the spread of infection from the ethmoidal sinuses via blood vessels or the lamina papyracea, or from the maxillary sinus via the infraorbital foramen. Orbital involvement presents with ophthalmoplegia (with or without pain), proptosis and partial or complete loss of vision. The finding of ophthalmoplegia and proptosis with ethmoidal or maxillary sinusitis should strongly arouse suspicion of ROCM. Ophthalmoplegia results from involvement of the oculomotor and abducens nerves at the orbital apex. Proptosis occurs owing to necrotic eschar at the orbital apex and oedema of the extraocular muscles. The direction of proptosis might provide a hint towards which sinus is involved (FIG. 1). Partial loss of vision suggests infiltrative or compressive optic neuropathy, whereas complete loss of vision suggests either posterior ischaemic optic neuropathy or central retinal artery occlusion.

When routed through the cavernous sinuses, intracranial infection leads to maxillary and mandibular nerve palsies and internal carotid artery thrombosis, pseudoaneurysm or, in rare cases, carotid cavernous fistula. From the sphenoid sinus, mucor travels across the clivus to the basal meninges and the basilar artery, leading to thrombosis or rupture with subarachnoid haemorrhage. Mucormycosis might also spread from the nasal cavity or the paranasal sinuses to the brain parenchyma, leading to cerebritis and abscesses.

Owing to the lack of preparedness for the COVID-19-associated ROCM outbreak, including the lack of availability of amphotericin B, the outlook could be bleak for many individuals. However, the situation also presented an opportunity to assess the effectiveness of other agents, particularly the newer azoles, posaconazole and isavuconazole, in the treatment of ROCM. Although a number of reports of treatment of ROCM are available from the pre-SARS CoV-2 era, these reports largely comprise single cases or small case series and expound the treatment preferences of individual physicians or units[9,10], possibly leading to bias. The COVID-19-associated ROCM outbreak presents a one-off chance for multiple disciplines and centres to join forces to document the clinical, imaging and laboratory features of the condition, examine risk factors and pathogenesis in the context of SARS-CoV-2 infection and trial different treatment approaches.

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Competing interests
The authors declare no competing interests.