

Mucormycosis and COVID-19: manifestations of the central nervous system and the ocular system

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As the COVID-19 pandemic continues to spread and cause high morbidity and mortality worldwide due to new variants, other pathogens continue to cause concern, such as mucormycosis, a deadly infection affecting the nasal cavity and sinuses. After inhalation of fungal spores present in the environment, the fungi first colonise and infect the nasal/sinus mucosa, before spreading. All-cause mortality rates for mucormycosis range from 40 to 80%, with rates varying according to underlying conditions and sites of infection. The causative agent of rhinocerebral mucormycosis is saprophytic fungi of the class Phycomycetes, order Mucorales and family *Mucoraceae*. These fungi include the genera *Mucor*, *Rhizopus*, *Absidia*, *Cunninghamella* and *Apophysomyces elegans*.¹

Mucormycosis has several clinical manifestations. The most prevalent is rhino-orbito-cerebral mucormycosis (ROCM) which begins with inhalation of spores allowing the fungus to spread to the sinuses. The infection rapidly spreads to adjacent tissues such as the sphenoid sinuses, orbits, cavernous sinuses and finally reaches the brain, and the clinical hallmark is tissue necrosis manifesting as a black eschar or discharge in the nasal or oral cavity.^{2,3} Angioinvasion of fungal hyphae into susceptible epithelium, coupled with host-specific conditions such as hyperglycaemia, ketoacidosis, iron overload and neutropenia, leads to endothelial damage, local haemorrhage, thrombosis, necrosis and subsequent dissemination.^{4,5}

Pulmonary, cutaneous, gastrointestinal, disseminated and health care-associated mucormycosis (HCM) are the other forms. Recently, an entity called COVID-19-associated mucormycosis (CAM) has been described,³ associated with

patients with COVID-19 infection with comorbidities, diabetes mellitus (DM) has been reported in more than 80% of the reported cases and studies, sometimes further associated with HbA1c > 10. Hypertension is the second most prevalent comorbidity in these patients. CAM can present from mild disease to severe and critical states. The use of glucocorticoids is one of the main risk factors that increase the rate of mucormycosis infection in COVID-19 as some of them have been used for this treatment (dexamethasone).^{6–8} The use of glucocorticoids in patients with COVID-19 has several effects: first, they increase blood glucose, depending on the dose and duration used; antagonise macrophage maturation and differentiation, leukotrienes produced by macrophages and pro-inflammatory cytokines IL-1, IL-6 and TNF; suppress the microbicidal activity of activated macrophages, and in addition, steroids inhibit neutrophil chemotaxis, lysosomal enzyme secretion and respiratory burst.⁹

It should be noted that the use of glucocorticoids in certain specific clinical settings in patients with COVID-19 has shown clinically important results in terms of recovery and reduced mortality, whereby the empirical and indiscriminate use of these drugs has been associated with negative results, and caution is recommended.¹⁰

Gupta *et al.*¹¹ in their study reported mucormycosis in 25.7% of patients and the same number were diagnosed during the course of their treatment with COVID-19; however, it may be a post-COVID-10 manifestation. ROCM has mainly been reported, and the paranasal sinuses, central nervous system (CNS) and ocular system have also been affected, the most common manifestations currently being facial pain (unilateral),

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ptosis, loss of vision, complete ophthalmoplegia, headache, intracranial complications (vasculitis).^{12–14} John *et al.*¹⁵ in their study performed a systematic review of the literature and found that 87% of patients had well-documented CAM, 83% were male and 71% were from India. Prompt treatment with aggressive surgical debridement and antifungal medication with amphotericin B is needed.^{12,16} Early diagnosis of ROCM is therefore of critical importance for patients with COVID-19 with sinusitis symptoms, particularly those with underlying diseases and those who have received systemic corticosteroids because prompt and aggressive treatment is essential for an optimal outcome.¹⁷

Given that ROCM appears to be the most prevalent clinical form of mucormycosis in COVID-19 cases, it is of great concern that direct spread from infected sinuses to the CNS may increase, and as previously described, cerebral mucormycosis is associated with high rates of death and disability.¹⁸ Emerging imaging is therefore of great importance in determining the diagnosis and extent of fungal infection. Magnetic resonance imaging (MRI) identifies sinonasal disease by sinus opacification with high attenuation content, thickening of the nodular mucosa and absence of fluid level. MRI can help us to focus on the current status of the patient's condition, as the black turbinate sign and periantral soft tissue infiltration are seen in the early stage of infection, and extranasal tissue infarction, optic nerve diffusion restriction and vascular invasion are features seen in more severe disease.¹⁹ COVID-19 is already a problem for patients with comorbidities, and with the lack of 100% effective treatment, the use of glucocorticoids is sometimes necessary to obtain improvement in this class of population.

CNS involvement in diseases such as COVID-19 and mucormycosis could lead to prolonged manifestations in these patients, so it is of utmost importance to continue close follow-up of recovering patients and for the medical community to continue to report these important cases to the literature, which may contribute to improve the clinical approach and management of patients.

It should be highlighted that secondary complications and mortality caused by ROCM should always be considered by health workers in patients with relevant past clinical history and the

characteristics mentioned above, specially in those widely documented countries of highest incidence such as India, allowing a quick and assertive diagnosis and also seeking to control conditions associated with the disease and establish the most appropriate treatment besides; these events demonstrate how much we should be careful when using glucocorticoids to avoid adverse effects in patients with comorbidities.

Author contributions

Michelle Ariana Polo Martínez: Conceptualisation; Data curation; Formal analysis; Investigation; Project administration.

Rita Fernanda Campo Jiménez: Funding acquisition; Investigation; Methodology; Project administration.

Jorge Andrés Castrillón Lozano: Methodology.

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