

## EDITORIAL

# Mucormycosis: A potential head and neck problem in COVID-19 patients

Mucormycosis is a rare fatal fungal infection that affects the nose and paranasal sinuses and may even extend to the orbit and the brain. The rhino-orbital-cerebral mucormycosis (ROCM) is the commonest form of Mucorales infection. The infection is usually transmitted by inhalation and causes tissue necrosis by angioinvasion and thrombosis.<sup>1</sup> The disease has a rapid course causing ischemia and gangrene of the affected tissue, and it mainly affects immunocompromised patients.<sup>2</sup> Before the pandemic of coronavirus disease 2019 (COVID-19), diagnosis of the disease was limited to individuals with low immunity such as patients with uncontrolled diabetes, end-stage renal diseases, hematologic malignancies, and/or organ transplantation. After the COVID-19 outbreak, many case reports of COVID-19-associated mucormycosis (CAM) have been published.<sup>3</sup>

The incidence of the disease is estimated to vary from 0.005 to 1.7 per million population worldwide in the pre-COVID-19 era, with special high incidence in India, which is about 0.14 per 1000 population.<sup>4</sup> Pal et al. described 10 CAM patients along 1.5 months in their institute, and they stated that the prevalence of the disease has risen more than twofold in India during the COVID-19 pandemic.<sup>5</sup> Also, Ravani et al. detected a dramatic increase in the number of patients recently diagnosed with ROCM at their Indian ophthalmology center compared with the pre-COVID-19 era.<sup>6</sup> The Indian government declared mucormycosis as an outbreak in May 2021.<sup>7</sup> Indeed, White et al. reported an incidence of invasive fungal infection of 26.7% among hospitalized COVID-19 patients.<sup>8</sup> In our university hospital, which is the largest tertiary referral center in our country, many CAM patients have been diagnosed recently. In the first 6 months of this year (2021), 16 patients were diagnosed to have ROCM, which is double the number seen in the same period of the previous year. All of them were recovered COVID-19 diabetic patients, and corticosteroids were included in their treatment protocol. Corticosteroids are usually used in the treatment of severe COVID-19 to reduce mortality, especially in hypoxic patients. Unfortunately, it has immunosuppressive and diabetogenic effects that may increase the risk of developing CAM.<sup>9</sup> In many studies, most reported CAM patients were diabetics, and corticosteroids were used for their treatment. Before the COVID-19 pandemic, the use of corticosteroids has been identified as a risk factor for mucormycosis. Skiada et al. found that 46% of their patients were on corticosteroids 1 month before developing mucormycosis.<sup>10</sup>

Mucormycosis has even been detected in some COVID-19 patients treated with corticosteroids in the absence of the traditional risk factors.<sup>9</sup>

COVID-19 could affect the cell-mediated immunity by decreasing the T lymphocytes, especially CD4+ and CD8+ cells.<sup>11</sup> However, many risk factors in severe COVID-19 patients may predispose to the occurrence of invasive fungal infection.<sup>3-5</sup> Decreased lymphocytic count is a feature in most COVID-19 patients. Mucorales-specific T cells (CD4+ and CD8+) secrete cytokines-like interleukin (IL)-4, IL-10, IL-17, and interferon gamma, which destroy fungal hyphae, and patients with mucormycosis show high levels of those specific T cells, so COVID-19 patients who already have lymphopenia might have a worse disease course than non-COVID-19 patients if they developed mucormycosis.<sup>12</sup>

A patient with ROCM is usually presented with offensive black crusty nasal discharge, facial pain, numbness, headache, blurred vision, ptosis, and/or proptosis.<sup>1</sup> Without early diagnosis and treatment, visual loss and/or brain infarction and even death could be the end result of the disease. Nasal examination usually shows black necrotic tissue in the nose and sinuses with possible orbital and/or brain involvement, and similar black tissue necrosis is often seen on the hard palate. Computed tomography imaging is usually essential in the diagnosis, and it shows bone destruction, and also, MRI could reveal brain infarction. Once diagnosis is suspected, a biopsy is taken routinely for direct microscopic examination and culture. Real-time polymerase chain reaction may sometimes be required to accurately detect fungi.<sup>1,13</sup>

Mucormycosis is usually treated with a combined approach: medical and surgical therapy. Control of diabetes is the most important step, with systemic antifungal medications such as amphotericin B (preferable to be liposomal type, to avoid nephrotoxicity) that should be given as early as possible. However, surgical debridement of the necrotic tissue using nasal endoscopy is performed in line with the medical treatment.<sup>3</sup> During debridement, it is crucial to clean the margins to stop the spread of fungal infection.<sup>1</sup>

The impact of COVID-19 on mucormycosis is still not fully understood. Several reports indicated a potential increased risk of developing mucormycosis in COVID-19 patients. John et al. reported that 94% of their CAM patients were diabetics.<sup>14</sup> Severe acute respiratory

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syndrome virus (SARS-CoV) has been found to cause damage to pancreatic islets, resulting in acute diabetes and ketoacidosis. Angiotensin converting enzyme 2 receptors that are the host of SARS-CoV-2 (the causative virus of COVID-19) were detected at a high level in pancreatic islets.<sup>14,15</sup> This finding may explain the diabetogenic state in some COVID-19 patients.

However, several other factors could increase the risk of development of mucormycosis among COVID-19 patients, such as corticosteroid therapy, which is being used in dyspneic patients, the use of broad-spectrum antibiotics, which may cause fungal flare-up, and hospitalization with possible nosocomial infection.<sup>2,3,14</sup> Also, generalized vascular endothelial damage has been found in postmortem autopsy in COVID-19 patients.<sup>16</sup> Endothelial damage is well known to be the first step in the pathogenesis of mucormycosis.<sup>14</sup> Furthermore, the tendency of SARS-CoV-2 infection to induce thrombosis may increase the serum iron, which consequently enhances the growth of the organism. Increase in serum ferritin and decrease in iron-binding capacity of transferrin in COVID-19 patients may provide the fungi with the iron needed for their growth. Also, ketoacidosis causes the same action as it decreases the blood pH that may increase the free iron, promoting fungal growth in diabetic patients.<sup>15</sup> All these factors could be involved in increasing the prevalence of mucormycosis among COVID-19 patients.


Because there are no studies that compared the prevalence of mucormycosis in the pre-COVID-19 versus post-COVID-19 eras, also in diabetic COVID-19 patients versus nondiabetic COVID-19 patients, and in those who received steroids versus who did not receive steroids and developed mucormycosis, it is difficult to establish the exact causal effect relationship between COVID-19 and mucormycosis in relation to diabetes and the administration of corticosteroids. However, high incidence of mucormycosis among diabetic patients, especially with ketoacidosis, has been documented; also, COVID-19 has been reported to cause ketoacidosis even in patients without a prior history of diabetes, and uncontrolled hyperglycemia and ketoacidosis are often observed with corticosteroid intake, so the misuse of corticosteroids could be a risk factor in causing mucormycosis in COVID-19 patients.<sup>15,17</sup>

In summary, mucormycosis is a severely aggressive fungal infection with a high mortality rate. Early management is crucial for this life-threatening illness. Classically, it affects immunocompromised patients, with uncontrolled diabetes being the commonest risk factor. Corticosteroid therapy for COVID-19 may increase the incidence of the disease. So, corticosteroids should be given only for severely affected cases, and they should be carefully monitored to detect its therapeutic effect with the lowest possible dose in the shortest duration. Other factors that may increase the risk of CAM may include hospitalization with possible nosocomial infections, the use of broad-spectrum antibiotics with fungal flare-up, high serum ferritin, vascular endotheliitis with thrombosis, and tissue necrosis, which may provide fertile media for fungal growth and impairment of leukocytic function. The diagnosis is suspected in high-risk patients with unilateral facial/orbital swelling or pain, ptosis, and/or proptosis. Tissue necrosis is often a late sign of the disease, and biopsy is an important step in the diagnosis. Control of diabetes, systemic antifungal, and surgical

debridement of the lesions are the ultimate treatments of the disease. Head and neck surgeons should be aware of increasing prevalence of mucormycosis among COVID-19 patients, especially in high-risk individuals, particularly those on steroid therapy.

## CONFLICT OF INTEREST

The authors declare no conflicts of interest.

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