

## Mucormycosis Infection in COVID-19 Patients in India: An Emerging Lethal Threat

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Opportunistic fungal infections have been reported to be associated with COVID-19 disease. Mucormycosis, an invasive fungal disease is being increasingly reported from India in patients with COVID-19 infection with comorbidities like diabetes. The increasing number of mucormycosis cases among Covid-19 patients during the current second wave of the pandemic is alarming owing to lethal sequelae of the disease.

The coronavirus disease 2019 (COVID-19) pandemic which started from Wuhan city of Hubei province, China since December 2019 and was declared the public health emergency of international concern (PHEIC) by World Health Organization (WHO) continues to be a significant problem worldwide [1,2].

The clinical profile of COVID-19 infection can range from milder symptoms to life-threatening pneumonia with associated bacterial and fungal co-infections [3]. Due to the associated comorbidities (e.g. diabetes mellitus, Tuberculosis, chronic obstructive pulmonary disease) and immunocompromising conditions (e.g. corticosteroid therapy, ventilation, intensive care unit stay), COVID-19 patients are very susceptible to acquire and develop severe opportunistic infections. There are many reports of severe opportunistic infections such as oropharyngeal candidiasis, *Pneumocystis jirovecii* pneumonia, pulmonary aspergillosis, bloodstream candida infections, etc. in COVID-19 patients [4,5]. Among the various factors associated with morbidity and mortality among the COVID-19 patients, opportunistic bacterial or fungal infections could worsen the clinical status of the patients and may lead to ARDS [6].

As of March this year, 41 cases of COVID-19-associated mucormycosis have been documented globally, with around 70% from India only [7]. The reports also suggest that actual number of cas-

es is going to be much higher and is expected to increase further, which is not surprising given the current wave of COVID infections in India.

In India, the prevalence of mucormycosis is approximately 0.14 cases per 1000 population, about 80 times the prevalence found in the developed countries [8]. COVID-19 has been associated with many fungal infections. The disease of mucormycosis is more often found in immunocompromised individuals and complications such as orbital and cerebral involvement are more expected in cases of diabetic ketoacidosis and with concomitant use of steroids. In India, the most common risk factor of mucormycosis is diabetes mellitus [9].

Sen., *et al.* [10] reported a case series of six COVID-19 cases with rhino-orbital mucormycosis who were managed at two tertiary ophthalmic referral centers in India between August 1 and December 15, 2020. Out of the six patients, one had concurrent COVID-19 and mucormycosis at the time of presentation, while five others developed mucormycosis during hospitalization in the course of treatment with systemic steroids given for management of COVID-19. All patients were known diabetics and the mean duration between the diagnosis of COVID-19 and development of mucormycosis was  $15.6 \pm 9.6$  (range 3 - 42) days. All patients underwent endoscopic sinus debridement, whereas two patients needed orbital exenteration. At the last follow-up, all six patients were alive, on antifungal therapy.

Patel., *et al.* [11] in another case series reported 12 cases of Rhino-orbitocerebral mucormycosis seen at department of ENT, GMCH, Nagpur, India from November 2020 to February 2021. Previous history of COVID-19 infection and treatment for the same was

found in 5 (41.67%) cases, concomitant infection in 2 (16.67%) cases and asymptomatic undiagnosed covid (antibodies positive) was seen in rest 5 (41.67%) cases. Commonest presenting complaint was nasal obstruction (66.67%) followed by loss of vision (33.33%) and swelling around eye (25%). Diabetes mellitus was the commonest co-morbidity (83.3%) with one patient (8.3%) having Pulmonary TB+CKD. At the end of 1 month, improvement in vision was observed in the 2 patients who had blurring of vision whereas all the 4 (33.33%) patients with complete loss of vision did not show any improvement. Improvement in the general condition with reduction in nasal necrotic tissue and inflammation was noted in all cases (100%).

Similarly, Sarkar, *et al.* [12] reported a cluster of 10 cases of clinically diagnosed orbital mucormycosis with concurrent COVID-19 illness seen between October and November 2020 at JIPMER, Pondicherry, India. All the patients presented with clinical features of orbital mucormycosis and COVID-19 was diagnosed subsequently on routine screening. All the patients in the series were known diabetics. Diabetic ketoacidosis (DKA) was apparent in four patients at presentation while five more patients developed DKA after the initiation of corticosteroid therapy given for management of COVID-19. Four patients expired within 1 month of the diagnosis whereas five patients had satisfactory systemic outcomes, but with irreversible vision loss. Only one of the patients had both ocular and systemic favorable outcome.

Mehta, *et al.* [3] reported a case of rhino-orbital Mucormycosis associated with COVID-19 in a 60-year male patient. The patient was a longstanding diabetic, with a positive RT-PCR for severe SARS-CoV-2. He received parenteral meropenem and oral oseltamivir with parenteral methylprednisolone for treatment of his COVID-19 infection. Over the course of the hospitalization, he developed signs of orbital cellulitis. Magnetic resonance imaging (MRI) of the revealed soft tissue swelling in the right pre-septal, malar, pre-maxillary and retro-bulbar regions with paranasal sinusitis. A nasal biopsy was performed which revealed broad aseptate filamentous fungal hyphae suggestive of mucormycosis, which was later confirmed on culture. The patient continued to deteriorate, required mechanical ventilation, and eventually required inotropic support and eventually died on day six of his admission. The authors concluded that extensive use of steroids/monoclonal antibodies/broad-spectrum antibiotics may lead to the development/

exacerbation of a preexisting fungal infection.

A study by White, *et al.* [13] from UK screened 135 adults with COVID-19 infection and reported incidence of invasive fungal infections as 26.7% among the COVID-19 patients (most common aspergillosis (14.1%) followed by yeast, usually candida (12.6%)). Patients with invasive fungal diseases had higher mortality (53% with v/s 31% without). Corticosteroid therapy and a co-morbidity of chronic pulmonary disease were found to be associated with a higher risk of the invasive fungal disease. The authors concluded that fungal disease occurs more commonly in critically ill, mechanically ventilated COVID-19 patients.

In conclusion, COVID-19 is associated with secondary infections, both bacterial and fungal, probably due to immune dysregulation. Mucormycosis is an opportunistic, life-threatening infection and patients with moderate to severe COVID-19 are more prone to develop it. Uncontrolled diabetes mellitus and systemic corticosteroid therapy increase the risk of invasive fungal infection with mucormycosis in COVID-19 patients who can develop it during the course of the illness or as a sequelae. High index of suspicion, prompt diagnosis, and timely management can improve survival and reduce the morbidity. All physicians and surgeons specially otolaryngologists and ophthalmologists should, thus, be mindful of the possibility of development of mucormycosis in patients with COVID-19 disease, particularly in those with comorbidities and on immunosuppressive agents.

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