

## Covid Era Fungal Rhino Sinusitis

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COVID-19 is a global health emergency and has affected millions of people worldwide. According to the WHO, the incidence rate of mucormycosis globally varies from 0.005 to 1.7 per million population. In our neighboring country India the prevalence is 80 times higher than the prevalence in developed countries. Case fatality is highest for the disseminated disease. This new corona virus disease continues to exhibit remarkable consequences globally along with atypical manifestations. This is associated with a significant incidences of secondary infections, both bacterial and fungal, probably due to immune dysregulation.<sup>1</sup> Though existing literature has shed much light on the native symptoms of the disease spectrum; addition of opportunistic infection has created an additional burden on healthcare resources. With the onset of COVID-19 pandemic, clinicians have seen an alarming rise in the number of cases of mucormycosis in post-infectious or active COVID-19 affected patients, which is many fold than the usual reported incidence of the disease in the pre-COVID setting.<sup>2</sup>

Mucormycosis is an opportunistic fungal infection caused by fungi of the order Mucorales, the most common of which is *Rhizopus oryzae*. Fungal spores are copious in the atmosphere and present in the soil, air decaying material and animal dung. They are inhaled and swallowed to cause infection. These spores can lead to a pathological affection if the environment is suitable for their growth and active invasion of tissues. Normally, inhaled fungi form a part of the normal sino nasal flora, but they are significantly destroyed by the immunological system.<sup>3</sup> However, in conditions such as prolonged antibiotics use, poor ventilation and moist environment as well as in immunocompromised patients, these immunological pathways may be disrupted, making fungal invasion more likely to make a morbid affection of tissues. Immunocompromised patients, such as those suffering from diabetes

mellitus (DM), malignancies, prolonged neutropenia, hematopoietic stem cell transplant/solid organ transplant recipients are at high risk of developing this disease.<sup>4</sup>

During the 3<sup>rd</sup> wave the otolaryngologists faces challenges with aggressive disease called rhino-orbito-cerebral mucor mycosis (deadly black fungus infection). Rhino cerebral mucormycosis is infection of the sinuses that can occur when a person with weak immune system breathes in fungal spores. Air enters the nose and paranasal sinuses which are air chambers found in the facial bones. The infection can spread from the sinuses into the orbit or brain, and then called rhino-orbito-cerebral mucormycosis. This fungi has the affinity for the adventitia of the vessel wall and causes endarteritis and thrombosis of the end arteries and hence the necrosis of the supplying organ.<sup>5</sup> Angioinvasion with infarction is the hallmark of invasive mucormycosis. The critical vessels in the vicinity of the disease, such as ophthalmic artery, sphenopalatine artery have been often found to be completely thrombosed with scanty bleeding intra-operatively. The resultant infarction contributes to the typical clinical findings of vision loss, sino nasal mucosal discoloration and necrosis of the underlying bone.<sup>6</sup>

Different reports underline the risk of opportunistic fungal infections like pulmonary aspergillosis and mucormycosis which accompany viral symptoms and may lead to death by invading multi organ system. The main reason behind invasive fungi infections is thought to be due to the impairment of innate defense mechanisms, such as ciliary clearance, and the lack of sufficient lymphatic immune response against fungal invasion during the pathophysiologic progression of deregulatory immune mechanisms in COVID-19-related acute respiratory distress syndrome (ARDS).<sup>7-8</sup>

COVID-19 and mucormycosis share risk factors, such as presence of diabetes mellitus, which can add to mortality. While immune suppression with steroids like dexamethasone may be essential in moderate to severe COVID-19, the use of steroids and the worsening glycemic control provide an opportunity for mucor to become invasive.<sup>9</sup> Mucor

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produces keto-reductase as a virulence factor facilitating them to grow in the acidic and glucose-rich environment produced in ketoacidotic states. In addition it has been postulated that the human pancreas could be a possible target for the SARS-CoV-2 virus which makes the  $\beta$ -cell infection and result in insulin resistance. This metabolic dysregulation, in previously non diabetic or well-controlled diabetic COVID-19 patients, might predispose them to develop mucormycosis. Furthermore airway epithelial damage in COVID-19 due to oxygen delivery devices, prolonged use of humidifiers without cleaning, use of industrial oxygen, multiple swab tests and steam inhalation burn injuries have been postulated to provide opportunity for fungus to invade lung tissues.<sup>7</sup>

Presenting symptoms depends on the extent of the infection, like nasal obstruction facial swelling, orbital complication (pain, swelling loss of vision, restricted eye movements) and intracranial complications (loss of consciousness, multiple or isolated nerve palsies).<sup>4</sup>

Treatment requires a multimodal approach involving antifungal therapy, surgical debridement, and reversal of immunosuppression to the degree possible. Hyperglycemia, diabetic ketoacidosis, and metabolic disturbances provide a favorable environment for fungal growth and should be aggressively addressed with glycemic control and electrolyte repletion. Concurrently, surgical debridement of necrotic tissue and antifungal therapy with liposomal amphotericin B or combination therapy with amphotericin B have been shown to improve survival.<sup>10</sup>

To conclude, Patients should be made aware of early symptoms, such as headache, numbness of face and blurring of vision which should prompt early seeking of advice from health professionals. On part of health workers it is of paramount importance to recognize the disease early in order to initiate prompt administration of antifungal treatment to lessen the complications, morbidity and mortality associated with black fungus. Diagnostic methods include biopsy and fungal staining (KOH mount), which remains the mainstay of laboratory diagnosis. Facilities where fungal culture and susceptibility testing are available can help to confirm the species of mucormycosis. Treatment initiation, however, should not wait for fungal culture results. Mucormycosis is difficult to treat. It may sometimes require both intravenous antifungal

therapy and surgical excision, thus necessitating a multidisciplinary team approach involving ENT, ophthalmologists, neurosurgeons and physicians. Liposomal amphotericin B is the drug of choice and needs to be initiated early. A take home message for prevention of COVID-associated mucormycosis is to focus on addressing the underlying risk factors more importantly reducing the inappropriate use of corticosteroids both by the community as self-medication and by the health provider unnecessarily and without proper indication for its use. A judicious COVID treatment protocol, high index of suspicion, close monitoring of high-risk patients and early institution of treatment can prevent case severity and reduce mortality.

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