Post COVID-19 Mucormycosis - from the Frying Pan into the Fire

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While our country battles with COVID-19, the issue of post COVID-19 sepsis has emerged as a significant problem. India bears the dubious distinction of being both the diabetes, as well as the mucormycosis, ‘capital’ of the world. COVID-19 and its treatment, against this backdrop, amounts to a recipe for disaster.

With an estimated 77 million cases in the adult population, diabetes is India’s fastest growing epidemic. A recent cross-sectional study from all states of India, revealed that 47% of Indians are unaware of their diabetic status and only a quarter of all patients achieved adequate glycemic control on treatment.¹ The unholy association between diabetes and the severity of SARS-CoV-2 infection has been repeatedly established in various studies from across the world.²

Mucormycosis sometimes appears as the diabetes-defining illness, and remains one of the most devastating complications in uncontrolled diabetics with mortality rates ranging between 40-80%. India contributes to 40% of the global burden of this “rare mould” infection as it is called in western literature, with an estimated prevalence of 140 cases per million population.³

Post COVID-19 sepsis is what occurs after SARS-CoV-2 has had a rampage in the human body and we are literally left picking up the pieces. It leads to a dysregulated innate immune response, ciliary dysfunction, cytokine storm, thrombo-inflammation, microvascular coagulation and eventual immune exhaustion. This cascade of events facilitates secondary bacterial and fungal infections especially in critically ill patients subjected to emergency invasive procedures, mechanical ventilation, CRRT, ECMO, poor nursing ratios, prolonged hospital stays and breaches in asepsis. Further, the use of corticosteroid treatment and anti-IL-6-directed strategies in these highly susceptible hosts along with high fungal spore counts in the environment creates the perfect setting for mould infections.

While COVID-19-associated pulmonary aspergillosis (CAPA) has received much international attention, the Indian epidemiology of invasive mould infections in the ICU reveals a significant burden of invasive mucormycosis.¹ This has recently emerged as a life threatening complication of COVID-19 in our country. Although the predisposing factors and pathogenesis are somewhat similar to that of other mould infections, certain unique characteristics and key distinguishing factors must be kept in mind in order to promptly suspect the infection, confirm the diagnosis and offer timely therapeutic intervention.

Mucorales are ubiquitous moulds, abundantly found in the environment on decaying organic matter. Various studies from hospitals across the country have revealed heavy mould spore counts even in hospital air due to predominantly hot, humid conditions in our tropical climate.⁵

Unlike CAPA, invasive mucormycosis has been observed even in patients with mild to moderate SARS-CoV-2 infections. The strongest predisposing factor appears to be hyperglycemia in undiagnosed or uncontrolled diabetics. Hyperglycemia leads to increased expression of the endothelial receptor GRP78, resulting in polymorphonuclear dysfunction, impaired chemotaxis and defective intracellular killing. An important virulence trait of Mucorales is their ability to acquire iron from the host which is an essential element for its growth. In conditions of ketoacidosis, free iron becomes readily available in the serum. This excess endogenous iron is efficiently taken up by the Mucorales through siderophores or iron permeases, further enhancing their virulence. These effects are greatly amplified by the use of corticosteroids and immunosuppressants in susceptible hosts. Corticosteroids themselves cause impairment in the neutrophil migration, ingestion, and phagolysosome fusion. Coupled with the potential implications of steroid-induced hyperglycemia, the diabetic COVID 19 patient receiving corticosteroids or other immunosuppressants is exceptionally vulnerable to the development of mucormycosis.⁶,⁷

The landmark RECOVERY trial published in June 2020 has served as a ‘licence’ to use steroids in patients with COVID-19. However, the fine print clearly revealed some important messages that we seem to have overlooked. Benefit was specifically shown with low dose, short duration dexamethasone in moderate to severe illness. Although, higher doses and longer durations may be used in exceptional cases due to compelling reasons, such patients should be evaluated for undiagnosed diabetes, checked for strict glycemic control and closely monitored for secondary infections. A cavalier attitude to the use of steroids should be discouraged at all costs.

The two most important manifestations of Mucormycosis in this setting are rhino-orbital-cerebral and pulmonary. Suspicion is based on subtle clinical and imaging clues, risk factors and disease development or progression while on any antibacterial or antifungal therapy that does not cover Mucor. Physicians need to have seen a ‘critical’ number of cases to recognize the signature of Mucor.

The clinical hallmark is tissue necrosis manifested as a necrotic lesion, eschar or black discharge in the nasal or oral cavity. Orbital, ocular and cranial nerve involvement are ominous

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signs that must be taken seriously. Alternative erroneous diagnoses lead to antibacterial and further steroid use which add fuel to the fire. Pulmonary Mucormycosis has certain radiologic findings which help to distinguish it from Aspergillosis. There is no biomarker for mucormycosis and hence a negative galactomannan and beta-d-glucan are useful pointers to rule out other mould infections. A false positive galactomannan due to generic piperacillin tazobactam use etc. can lead to the erroneous diagnosis of invasive aspergillosis. Although challenging, the need to distinguish Mucor from bacterial infections and from aspergillosis in a timely fashion is of essence. Treatment with voriconazole for suspected invasive aspergillosis increases the pathogenicity of Mucor with obvious dire consequences.

Rapid diagnostic methods include biopsy, KOH mount and Calcofluor stain. Mucor is difficult to routinely culture. Biopsy remains the mainstay of diagnosis and the benefits of the procedure outweigh the risk, even in a ‘difficult to access’ location or in the presence of coagulopathy.

Treatment principles include antifungal agents, surgical debridement, reversal of underlying predisposing factors and adjuvant therapy. Amphotericin B has been the standard of treatment for invasive mucormycosis. COVID-19 patients may have developed acute on chronic renal failure which may be mitigated by switching to a less- or non-nephrotoxic alternative. Therefore Posaconazole or Isavuconazole may have to be used. The latter has the added advantage of shortening the QT interval which may have been affected by HCQ, Azithromycin which many patients still continue to receive. Surgical debridement, the earlier the better, is pivotal in the management of mucormycosis. The optimal time of surgery to reduce the operative risk to the patient with COVID-19 and the risk of transmission to the operating team is a contentious issue. Replication competent virus has not been recovered from patients with mild to moderate illness after ten days, from patients with severe illness after fifteen days or from any critically ill patient after twenty days.⁸

Adjuvant therapy with caspofungin, deferasirox, statins, aspirin, and hyperbaric oxygen may have to be considered. Mucormycosis needs to be actively managed by a team which includes members from almost all departments in the hospital. Therapy is toxic and very resource intensive. In a recent Indian study, 24.3% patients left the hospital against medical advice due to the anticipated cost, morbidity of surgery and prognosis.⁹ Mucormycosis developing in the post COVID-19 setting ‘breaks the back’ of a patient’s family that is barely recovering from a treacherous viral infection. This scenario is nothing short of ‘RECOVERY from the frying pan and into the fire.’

References