COVID-19-Associated Mucormycosis: A Battle Against Fatal Menace

Our understanding of coronavirus disease 2019 (COVID-19) is still evolving, and many new facets are coming to limelight. Considered initially to be a respiratory illness, it is a multisystemic disease with a large toll on the nervous, gastrointestinal, hepatic, and genitourinary systems. COVID-19-associated mucormycosis (CAM) is an emergent opportunistic infection that has commanded global attention, more so during the second wave of COVID-19.[1-3] While the correlation between the two is understandable, the underlying pathophysiological mechanisms of CAM are still elusive.

A large number of cases with varied presentations are seen during the second wave of COVID-19 which in India began from Feb 2021 onwards. Two articles published in Jan-Feb 2022 and one in the current issue of the journal have tried to explore this mystery.[4-6] The estimated prevalence of mucormycosis in India is 70 times more than the global prevalence, particularly in the states of Gujarat, Maharashtra, and Karnataka.[7-9] Most of these cases are associated with rhinosinusitis involving the eye and/or brain (rhino-orbital/rhino-orbito-cerebral).[10,11]

The surge in the number of CAM cases after second wave can be attributed to a combination of factors like environmental conditions, causative agents, host factors, and others contributed by health system.[1,8,12] Immune dysregulation that occurs in the setting of severe acute respiratory syndrome–related coronavirus 2 (SARS-CoV- 2) infections has been postulated to increase the risk of invasive mycosis during the second wave of COVID-19.[5,10] Environmental factors need to be researched in detail. Tropical weather and bad sanitary conditions favor the growth of fungal spores. In a multicenter study across 11 hospitals across India, Mucorales were isolated from 11.1% of the air-conditioning vents and 1.7% of the patients' used masks.[13] In addition, they also grew Mucorales from 21.7% indoor and 53.8% outdoor air samples. The use of nonsterile water for humidification of oxygen and improper disinfection of oxygen dispensers also favor the growth of fungus.[2,5,14] Use of industrial oxygen was quite rampant in resource-poor countries during the early phase pandemic and that might have contributed to a high incidence of Mucor. Thus, regular surveillance and following safe and hygienic practices are utmost essential.

In addition to conventional risk factors such as uncontrolled diabetes mellitus with ketoacidosis, hematological and solid malignancies, solid organ and bone marrow transplantation, and antineoplastic and immunosuppressive drugs, new risk factors are also emerging. They include hypertension, chronic cardiovascular diseases, renal failure, liver failure, obesity, use of interleukin-6 blockers, high ferritin leading to iron overload, acidosis, intravenous drug abuse, and prolonged hospitalization.[1-3,11,15] In recent studies, it was observed that a heavy dose of zinc supplementation either as self-administration by the patients or as over-prescription by the treating clinicians can increase the risk for Mucor.[7,16]

Irrational and prolonged use of steroids and unnecessary hospitalization were quite common during the pandemic. In various studies, inappropriate steroid use was observed in more than 50% of the patients.[4,8,17,18] A meticulous adherence to low-dose steroids as per protocol coupled with good glycemic control will be a welcome step in the risk reduction of CAM.[19] Surprisingly, we are also witnessing a large number of younger patients with CAM during the second wave of COVID-19 harboring no known risk factors or other co-morbidities.[8]

Management

The predominant pathology in CAM is angioinvasive fungi causing necrotizing tissue damage and a prothrombotic state resulting in thrombosis in surrounding vessels such as cavernous sinus and internal carotid arteries. Thus, the occurrence of stroke is higher with CAM than with non-COVID mucormycosis.[5] Common post-COVID neurological manifestations are stroke, acute disseminated encephalomyelitis (ADEM), Guillain–Barre syndrome, and mononeuropathies.

Clinical suspicion of mucormycosis should be supplemented with the liberal use of imaging of paranasal sinuses, orbits, brain, and intracranial vessels to develop a risk-based treatment algorithm.[1,4] While computed tomography (CT) is preferable to delineate bone destruction and other changes, magnetic resonance imaging (MRI) is useful in demonstrating the optic nerve, and intracranial and vascular invasion. Tissue sampling for specific identification of fungi and histopathological analysis of diseased tissue is almost a must for treatment planning.[20]

To reduce mortality and morbidity of CAM, the treatment should be prompt and includes a combined approach of antifungal therapy and surgery.[7] Systemic antifungal therapy with high-dose liposomal amphotericin B is the gold standard and can be followed with broad-spectrum triazoles such as posaconazole and isavuconazole if needed.[5,20] Endoscopic or surgical debridement and orbital debulking should be considered at an early stage as drugs do not reach the necrotic tissue. In addition to these, correction of underlying metabolic abnormalities such as hyperglycemia, ketosis, and acidosis is crucial to improve outcomes.[1,5,15] Other novel therapies like statins and other modes of administration of Amp B are under research.

CAM is a rapidly progressive infection that is fatal if left untreated.[17] Mortality with CAM ranges between 29% and 49%, and poor prognostic factors are disseminated mucormycosis with cerebral involvement, shorter duration of symptoms, delay in starting treatment, uncontrolled diabetes, and prolonged steroid treatment.[1,11,21] Grading of illness based on tissue necrosis, degree of inflammation, fungal load, angioinvasion, and biomarkers will be of additional help to prognosticate the CAM. Larger studies are needed to delineate prognostic markers and outcomes on other systems.

Conclusions

During the COVID-19 pandemic, the surge of CAM has become a serious concern, particularly in India.[3,7] Double- and triple-mutant variants of SARS-CoV-2 have emerged in India during the second wave of COVID-19, which are more dreadful and are doubted to play a mightier role in the CAM surge. Resultant immune system defects with COVID-19 need to be studied to understand its pathophysiology. Better knowledge and understanding of the risk factors and their management play a key role to reduce mortality and morbidity.[2,11,15] Thus, there is a need to initiate an awareness program among treating physicians.[4] The risk of CAM can be decreased by early suspicion, vaccination against COVID-19, optimal use of corticosteroids and monoclonal antibodies, meticulous glycemic control, and adequate attention toward ventilators and tubing.[5,19] The role of prophylactic antifungal agents or other measures in this situation is a subject of research.

As most studies are from tertiary care hospitals, it is possible that we are missing a large number of asymptomatic or oligosymptomatic cases with cerebral involvement. Case registries at national and international levels are necessary to study new predisposing factors, clinical features, treatment strategies, prognostic indicators, and long-term effects.

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