

Diabetes, COVID-19 and Mucormycosis: Unanswered Questions!

India is witnessing a steep surge of COVID-19 along with increasing mortality from SARS-CoV-2 infection. This is propounded by an unprecedented outbreak of mucormycosis infections amongst COVID-19 patients. Although mucormycosis is a rare disease, the pre-COVID prevalence of mucormycosis in India was about 80 times that of developed countries (approximately 140 cases per million population in India compared to 0.0007–1.70 per million globally).^[1] A recent systematic review identified 101 reported cases of mucormycosis in COVID-19 worldwide including 83 from India.^[2] This is likely the tip of the iceberg as no national surveillance exists for mucormycosis, although electronic/print media is full of reports of mucormycosis. Recent country-wide data suggest close to 30,000 cases of mucormycosis during COVID-19 pandemic in India as of June 16, 2021.^[3] As a result, mucormycosis was declared a notifiable disease under the Epidemic diseases act, 1897 on May 20, 2021 by many states; and renewed health advisory for early screening, diagnosis, and management of mucormycosis in COVID-19.

Have fungal infections come as a surprise in the COVID-19 pandemic? Looking back, the incidence of fungal infection during the SARS-CoV infection in 2003 was 14.8%–27%, contributing to maximum mortality (25%–73.7% of all causes of death) among patients with severe acute respiratory distress syndrome.^[4] A high probability of increased incidence of fungal infections in COVID-19 in affected or recovered patients is unlikely to be unprecedented considering considerable biological similarities between SARS-CoV-1 and -2 requiring prolonged hospitalization. The co-occurrence of diabetes and glucocorticoid use in COVID-19 has perpetuated fungal infections. People with diabetes are known to have adverse outcomes from COVID-19 with higher mortality. Following the RECOVERY trial, 10-day high-dose steroid course in severe or critically ill COVID-19 patients reduced ICU stay and mortality.^[5] Despite this, many patients with severe COVID-19 require prolonged ICU stay and mechanical ventilation leading to the continuation of glucocorticoids (GCs) beyond the second week.^[6] Prolonged supraphysiological doses of GCs predispose patients with compromised immunity secondary to diabetes for opportunistic fungal infections including potentially life-threatening mucormycosis. The question remains that steroids have been used for decades in supraphysiological doses for varied diseases, but mucormycosis infection surge has not been observed prior. Is it related to a differential immunocompromising (high doses used in COVID-19) versus anti-inflammatory doses (relatively less) of GCs. Secondly, immune-modulators targeting interleukin-6 (IL-6) like tocilizumab used for the management of COVID-19 have

also been associated with late infections like mucormycosis.^[7] Otherwise, excessive steam inhalations, use of nasal canula for oxygen delivery and injury during intubations may also predispose for mucormycosis.^[8]

Why is that India is ravaged with mucormycosis in the COVID-19 pandemic, whereas rest of the world has only isolated reports of mucormycosis? Is it secondary to swelling numbers of COVID-19 patients in the second wave in India with potentially more virulent strain B.1.617.2, when rest of the world is observing a downtrend? Or is it due to health care delivery issues including hasty makeshift COVID care facilities with possible unsterilized hospital linen, non-sterile medical devices including humidifiers used for inhaled oxygen, usage of industrial oxygen because of acute shortage of medical oxygen, tropical climate, and predominant agrarian population? Treatment-related factors including uncontrolled hyperglycemia with mean HbA1c 8.48% among Indian diabetes patients, an increasing number of COVID-19 patients on supraphysiological, and prolonged course of glucocorticoids may all predispose to opportunistic fungal infections.^[9]

Is diabetes more prevalent in COVID-19 patients predisposing them to mucormycosis? *Mucor* being an opportunistic fungus causes infection in an immunocompromised host and diabetes is considered the most common risk factor compromising immunity especially in resource-poor setting with poorly controlled diabetes. The high prevalence of diabetes amongst COVID-19 patients is questionable, as the pooled prevalence of diabetes in COVID-19 is 11.5% (9.7–13.4),^[10] almost similar to the general population in urban India (10.9% and 14.2%) that is more ravaged by COVID-19.^[11] Similar observations for the comparable prevalence of diabetes in COVID-19 patients have been observed from many countries except Iran.^[12] However, the high dose of steroids in COVID-19 predisposes these patients for worsening glycemia further dampening the immune functions and pose greater risk of developing fungal infection including mucormycosis. Though long-term usage of glucocorticoid is known to be associated with opportunistic fungal infections; but even a shorter course of GCs (5–14 days) may induce mucorale infections in people with diabetes.^[13] The co-occurrence of COVID-19 and diabetes further predisposes for mucormycosis due to increased availability of free iron consequent to ferritin release from hepatocytes and macrophages and dissociation of porphyrins from iron of hemoglobin; and acidosis milieu in diabetic ketoacidosis (perpetuated by steroid) causing proton-mediated displacement of ferric iron from transferrin.^[14] Moreover, angio-invasive mucormycosis causes extensive microvessel

thrombosis that may be propounded by endothelial dysfunction in diabetes and increased pro-inflammatory cytokines in COVID-19.^[15] An overzealous multi-vitamins containing zinc supplementation may increase free radical availability plausibly predisposing for fungal infections. On the other hand, zinc deficiency increases susceptibility for respiratory tract infections (RTI) and its supplementation is known to enhance anti-viral activity preventing (RTI).^[16]

Mucormycosis being a potential life-threatening infection require intensive care facilities, extensive surgical resection, and prolonged medical therapy with amphotericin-B. A wider dissemination of information by the government agencies regarding symptomatology for an early domicile recognition of symptoms by the patients, an early referral, equitable distribution of health care resources including diagnostic facilities (CT scan and histopathology laboratory for fungus identification), adequate supplies of anti-fungal drugs, availability of operation facilities and surgical expertise for treating fungal infections at peripheral centers are some of the measures that may be useful to curb the epidemic within pandemic. Despite raging numbers of mucormycosis in COVID-19, more evidence is required from large studies to attribute a possible association between two entities.

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