COVID-19 associated Mucormycosis (CAM): risk factors and mechanisms of disease

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SUMMARY

The spike in cases of COVID-19 associated mucormycosis (CAM) reported from India during the pandemic surge in early 2021 may be due to an unfortunate alignment of multiple risk factors, chiefly dysglycemia and steroid therapy superimposed on high background prevalence.

ABSTRACT

The severe surge of COVID-19 cases in the Indian subcontinent in early 2021 was marked by an unusually high number of cases of COVID-19 associated mucormycosis (CAM) reported during this period. This is significantly higher than predicted based on available data about prevalence or risk factors for this condition. This may be from an unusual alignment of multiple risk factors for this condition. There is high background prevalence of mucormycosis in India probably from high prevalence of risk factors, including undiagnosed or poorly controlled diabetes. COVID-19 induced immune dysregulation, and immune suppression from steroid therapy increase the risk. The role of environmental exposure is unclear. System factors like lack of access to healthcare during a pandemic may result in delayed diagnosis or suboptimal management with potentially poor outcomes. This is a review of currently identified risk factors and pathogenesis of CAM in a pandemic surge.

Key words: Mucormycosis, zygomycosis, COVID-19, rhino-orbito-cerebral, steroid therapy

INTRODUCTION

The COVID-19 pandemic's devastating surges across the world have overwhelmed healthcare facilities and resulted in dramatic increases in excess mortality. Secondary bacterial and fungal infections in patients hospitalized with COVID-19 pneumonia contribute to increased morbidity and mortality (1, 2, 3). There have been reports of COVID-19 associated pulmonary aspergillosis (CAPA) reported in critically ill patients with COVID-19 (2). The recent surge of COVID-19 cases in India has been marked by an unexpected increase in cases of mucormycosis reported in the context of COVID illness, with an estimated 2.1 fold increase in cases as compared to pre-pandemic period (4).

The clinical course of mucormycosis is protracted, and treatment is challenging and often includes surgery and prolonged antifungal therapy. Mucormycosis is associated with high mortality even with standard care (~50%, and >90% with disseminated disease) due to the angioinvasive nature of infection which can cause tissue necrosis due to thrombosis and dissemination of infection. The surge in cases in India is in a setting of widespread healthcare access shortages, including access to specialty surgical care and shortage of antifungal agents. Hence prevention and risk mitigation are very important. Herein we review potential risk factors and pathogenesis of COVID-19 associated mucormycosis (CAM).

Risk factors of non-COVID-19 mucormycosis

Pathogens associated with mucormycosis are filamentous mold belonging to class Zygomycetes and order *Mucorales.* They are thermotolerant environmental saprophytes found in wet, damp environments, including soil, decaying organic and vegetable matter. Though many genera/species can cause mucormycosis, *Rhizopus* spp., *Lichtheimia* spp., and *Mucor* spp. account for 75% of reported cases (4). Mucormycosis is rare, but sporadic cases and small outbreaks have been reported all over the world. Risk factors for invasive disease

in non-COVID-19 occurrence include prolonged neutropenia, especially in setting of hematologic malignancies, prolonged steroid therapy, uncontrolled diabetes and diabetic ketoacidosis, iron chelation therapy, chronic kidney disease as well as inoculating breach of skin barrier due to puncture wounds, including wounds sustained in blast injuries or natural disasters, burns, surgical wounds, as well as injection drug use (5).

COVID-19 related mucormycosis

Data on risk factors and clinical course of CAM are beginning to be reported (4, 6). While most published cases of CAM were sinonasal limited (6), rhino-orbital spread was reported in 41-63% (4, 6, 7) and rhino-orbito-cerebral (ROC) spread was reported in 21-23%. Less frequently, pulmonary disease (8.6%), and disseminated disease is reported (2%).

Median time to CAM diagnosis from COVID-19 onset was 13-18 days (4, 7). Demographic and underlying risk factor data show male predominance (80%), underlying or current diabetes in 60-80% and steroid use in 76-78%. Of note only 33.6% patients in one multicenter study were reported to have received steroids at appropriate level per dose recommendations from the RECOVERY study (4). In a third of patients steroids were not indicated. Hypoxemia due to COVID-19 and inappropriate glucocorticoid administration were associated with development of CAM.

A high degree of clinical suspicion needs to direct the diagnostic evaluation, especially in hospitalized COVID 19 patients with moderate to severe disease. Nasal or facial pain or swelling, nasal congestion or discharge and eyelid swelling may guide tissue sampling in ROC disease (7). Available data indicate diagnosis by direct microscopy of tissue in 83% with aseptate hyphae noted in tissue samples (4). This is similar to non-CAM. Tissue biopsies sent for histopathologic identification showed aseptate hyphae in 76-92% (4,7). Cultures were positive in 53% as compared to 39% non-CAM in one study. The most common

isolated Mucorales included *Rhizopus* spp, *Mucor* spp, *Lichtheimia* and others. Molecular tests or sequencing has been used rarely. Coinfection with other bacteria or fungi is rare.

Mortality was 31-44%. Increasing age, need for intensive care unit admission and orbito-cerebral extension were associated with mortality for CAM (4).

High baseline prevalence of non-COVID mucormycosis in the developing world may affect risk for CAM

The global prevalence of mucormycosis is unknown, especially in the developing world. Limited diagnostic sensitivity of conventional diagnostic methods may limit accurate identification of cases. Modeling data has indicated a prevalence of 14 cases per 100,000 population in India with 38% mortality. Though these data may be limited by sampling bias and population data may be lacking, this is nearly 70 times the global prevalence of 0.2/100,000 (8). Rhino-orbito-cerebral infection (~45-74% cases) in poorly controlled diabetics is the most common presenting syndrome. *Rhizopus* and *Apophysomyces* are the most commonly isolated pathogens (9). The humid and hot tropical climate which allows the mold to thrive in environment (10), increasing prevalence of diabetes in India, increased access to healthcare and identification of cases may all be contributory to an increasing incidence of mucormycosis in India in the past 2 decades (11).

A lack of population data limits prospective risk assessment, but studies from India estimate disease prevalence of 0.16% in patients with diabetes admitted to one referral center (12) and 1.2% amongst renal transplant recipients (10). A recent multicenter retrospective study of COVID-19 associated mucormycosis (CAM) among hospitalized COVID-19 patients estimated prevalence at 0.27% (4). The assumption based on these data would be that hospitalization for COVID-19 poses an intermediate risk between diabetes and solid organ transplantation, though high background prevalence of diabetes mellitus in India may be an

additive risk for CAM. At its peak, India reported 3.7 million active cases of COVID-19 (13). Assuming 15% would require medical attention or treatment, and symptomatic COVID-19 and its treatment predisposed patients to mucormycosis, approximately 0.5 million SARS-COV2 infected patients from this surge would be at risk for CAM. Based on the above prevalence data for diabetic and transplant patients, we would estimate approximately 900 (diabetes level risk) to 6,500 (transplant level risk) incident cases to occur as a consequence of this COVID surge. Since 40% cases may be seen in COVID recovered patients (6), this estimate is likely higher. As of June 16, 2021, 27,142 cases of mucormycosis (14) have been reported in India in the midst of its COVID surge. This high number would suggest that the predisposition is cumulative and multifactorial beyond risk predicted by individual host factors like dysglycemia, steroid or immunosuppressive therapy.

Role of Diabetes

There is a bidirectional relationship between COVID-19 and diabetes. There is an increased risk of severe COVID-19 with diabetes including need for critical care and mechanical ventilatory support and death (15). COVID-19 has also been associated with new-onset diabetes and severe metabolic complications of prior diabetes, like diabetic ketoacidosis. This may be due to decreased insulin secretion, impaired glucose utilization due to inflammation or stress counter regulatory response.

Nearly 54–76% of the non-CAM cases reported from India are in patients with uncontrolled diabetes, with or without ketoacidosis (9,10,11). Up to 84% of patients with ROC mucormycosis had uncontrolled diabetes in one series (9).

Preexisting or underlying diabetes is reported in 62-80% CAM patients, with poor control reported in 41-67% (7,16) of cases, and with diabetic ketoacidosis in 15-21% (4,6). Median hemoglobin A1C in one report was 9.6% (7). India has the second highest prevalence of

diabetes mellitus (DM) in the world with over 65 million people with DM (17). The large majority of diabetics in India are poorly controlled and many remain undiagnosed and mucormycosis has been described as a DM defining illness in 12-31% cases (5, 18). This figure was 21% in the CAM cohort (4).

Hyperglycemia glycosylates ferritin and transferrin and elevated beta hydroxy butyrate (BHB) in ketoacidosis lowers serum pH. Both these changes seen in uncontrolled DM diminish affinity of iron binding proteins, allowing unbound iron to circulate in blood and the free iron is then utilized by Mucorales (19). Low serum pH also diminishes the chemotaxis and phagocytic effect of macrophages and neutrophils by oxidative and non-oxidative pathways. Elevated glucose, iron, and BHB mediated metabolic acidosis may increase expression of host receptor glucose regulator protein 78 (GRP78) and the fungal ligand which belongs to the spore coating (CotH) protein family. The spore germinates and germlings adhere to and invade endothelial cells by specific recognition of GRP78. This facilitates angioinvasion of Mucorales. BHB-related acidosis exerts a direct effect on both GRP78 and CotH expression (an effect not seen with lactic acid) and an indirect effect by compromising the ability of transferrin to bind iron. Clinical and animal models show that ketoacidosis does not predispose to Aspergillosis (20). Elevated glucose, iron, and BHB also suppress T lymphocyte activity and interferon-γ (IFN-γ) and phagocyte mediated killing (23) creating a unique environment for the fungus to thrive.

Steroid therapy

Corticosteroids are indicated for the treatment of hospitalized patients with COVID-19 pneumonia who require supplemental oxygen and higher levels of respiratory support (21). Corticosteroid therapy is a risk factor for mucormycosis. In cancer patients, steroid use with a cumulative dose of prednisone >600 mg in the 4 weeks prior was a risk factor for

mucormycosis (22). Shorter courses of steroids for exacerbations of chronic obstructive airway disease have been associated with mucormycosis.

The oxidative and non-oxidative killing by neutrophils and monocyte/macrophages are the main line of defense against spores and germinating hyphae in the lung. Glucocorticoids suppress several polymorphonuclear (PMN) leucocyte functions, such as margination, chemotaxis due to decreased expression of adhesion molecules on endothelial cells, and phagocytosis. They suppress the oxidative burst and free radical generation, degranulation and decrease apoptosis of dysfunctional neutrophils (23). Steroids cause reversible monocytopenia, and impair phagocytosis by resident macrophages, as well as maturation, chemotaxis, and phagolysosome fusion of monocyte/macrophage system. Moreover, glucocorticoids decrease the secretion of proinflammatory cytokines like interleukin-1 (IL-1), IL-6, and tumor necrosis factor-alpha (TNF-α) by macrophages (23).

Glucocorticoids also cause lymphopenia and T lymphocyte dysregulation with a TH2 predominant cytokine response which causes decrease IL-2, IL-12, TNF-α, and IFN-γ which causes suppression of phagocyte effector cell function and poor outcomes of invasive fungal infection (23).

They may aggravate hyperglycemia in diabetic patients or induce diabetes mellitus in predisposed patients by causing beta cell dysfunction acutely and causing insulin resistance in skeletal muscle and adipocytes with continued use. They may also attenuate clinical signs of infection like fever by blocking prostaglandin synthesis, radiologic signs, and contribute to delayed diagnosis (23).

COVID-19 was treated with corticosteroids in 76-87% in published data on CAM (4, 7). There are anecdotal data about widespread inappropriate overuse of steroids in management of COVID-19, including use in ambulatory management. Other immunomodulatory therapy

used to manage the inflammatory phase of COVID-19 may contribute to more prolonged or severe immunosuppression and potentially elevate risk. In published cases of CAM, tocilizumab was administered in 2-4% cases (4, 6).

COVID-19

While COVID-19 treatment and associated risk factors may predispose to CAM, it is not clear if the illness itself may elevate risk. COVID-19 pneumonia can cause alveolar epithelial damage. The extracellular matrix proteins may be exposed, and it has been shown that *Rhizopus* spores adhere to laminin and type IV collagen (24). In prospective case control studies, serum GRP78 levels have been shown to be increased during COVID-19 pneumonia as compared to healthy controls and this may be a marker of stress response and endothelial dysfunction (25). The role of GRP78 as an endothelial receptor for the fungal ligand CotH and its role in angioinvasion has been mentioned above. In accordance a positive correlation exists between C reactive protein levels and GRP78 levels. COVID-19 causes lymphopenia which correlates with severity of illness. Lymphopenia has been shown to be a risk factor for invasive fungal infections (22).

The inflammatory response to SARS-COV-2 infection is characterized by an increase in cytokine response, particularly secretion of IL-6. It is thought that this stimulates ferritin and hepcidin synthesis and may lead to sequestration of iron in macrophages. Since excess intracellular iron has been associated with increased risk of mucormycosis, the hyperferritinemic state may putatively increase risk though this has not definitely been proven. In addition, the hyperferritinemic state can sustain a feed forward loop of hyperinflammation and also modulate the lymphocyte response (26). Indeed, there have been case reports of mucormycosis in hyperferritinemic syndromes like hemophagocytic lymphohistiocytosis (27) and adult onset Still's disease (28).The prothrombotic state

associated with COVID-19 may putatively help propagate angioinvasive complications associated with CAM like cavernous sinus thrombosis or stroke.

COVID-19 has caused delay or avoidance of care for non-COVID-19 health conditions including those needing urgent or emergent care. Access issues due to state or locally imposed lockdowns, widespread hospital bed shortages, disruptions of support systems with multiple household infections may all indirectly contribute to delayed recognition and treatment. Infection prevention measures may contribute to delayed recognition of CAM as physician encounters could be abbreviated. Nasal stuffiness, discharge, anosmia could be from COVID-19 infection. It is known that delayed diagnosis may contribute to increased risk of mortality with mucormycosis.

Environmental

Saprophytic fungi are abundant in the environment including soil, dust, and plant matter. Whether environmental factors play any role in the risk of mucormycosis is not clear. Indoor and outdoor dust pollution in India is an important issue and hospital dust has been shown to harbor dematiaceous fungi from environmental sampling data from India (29). Aeromycological analysis in a community and hospital setting from India reported the isolation of pathogenic Mucorales in air samples (30). Mucorales are abundantly isolated from Indian alkaline soil with low nitrogen content (31). Construction and renovation may increase airborne fungal spore load. A study from South India reported that 29% of cases due to *Apophysomyces* species were nosocomial in origin (32). In other studies, nosocomial origin of mucormycosis has been attributed to 9% of reported cases (11). Contaminated medical devices have been implicated in 41% of outbreaks related to Mucorales and contaminated air in 31% (33). Also, in developing countries, air filters of air conditioning units may be colonized with fungi (26%) with potential increased risk of fungal infection though this risk

is difficult to estimate (34). In outbreak of deep seated invasive fungal infections, these filters have been thought to have played a role (35).

It is not clear if equipment used for oxygen administration can be contaminated with fungal organisms or whether this contributes to infection risk. The survival of Mucorales in high oxygen environment may not be optimal and only 55% of hospitalized patients with CAM were noted to be hypoxemic needing oxygen supplementation (4,7). The risk of water contamination with invasive fungal species seems to be low (33) and so nebulizer fluids or inline humidifier tubing used in ventilator circuits would be considered to be unlikely to be a source for these infections. The current surge of COVID-19 in India has led to widespread oxygen shortages and increased use of impromptu oxygen systems including oxygen concentrators in place of piped central oxygen. These concentrators draw ambient air and compress it and extract oxygen to administer to patients. It is unclear if dusty environmental conditions within locations where COVID-19 patients are cared for or where such portable temporary oxygen supply systems may be housed, and may draw ambient air from, may be contributing to cases. Negative-pressure rooms may be a risk factor for invasive mold infections, related to the potential to suck in and concentrate dust and mold spores in these rooms from relatively higher pressure corridor or ante rooms (36).

Hospitals caring for patients with COVID-19 need to have systems to limit environmental exposure to fungal pathogens to mitigate the risk. This would include dust control, limiting renovation and construction near patient care areas, filtration of indoor air for units where critically ill patients are housed if feasible, installation of inline filters and regular maintenance and cleaning of temporary portable oxygen systems. In addition, if multiple cases are seen in a single unit appropriate investigation including determining trends, exposures and appropriate environmental assessments should guide prevention and control measures and also future surveillance (37).

Conclusion:

The unusually high number of cases of CAM seen in the context of the second surge of COVID-19 in India may be from an alignment of multiple risk factors. High background prevalence of mucormycosis in India, undiagnosed or poorly controlled diabetes, COVID-19 induced immune dysregulation, and therapies like steroids which cause immune suppression, in the setting of shortage of healthcare access amidst a pandemic surge created a perfect storm for this to snowball into a public health crisis. Preventive measures may need to focus on identification and optimal management of risk factors for CAM including aggressive glycemic control, avoiding steroid overuse and possibly environmental measures.

NOTES

JWB reports consulting fees from Pfizer. JVC and SN do not have any conflicts of interest to report that are relevant to the submitted manuscript. The author(s) received no financial support for the research, authorship, and/or publication of this article.

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LEGEND FOR FIGURE 1:

Figure 1: Proposed mechanisms of increased risk of mucormycosis due to SARS-COV2 infection.

IL-6, Interleukin 6; DKA, diabetic ketoacidosis; BHB, beta-hydroxy butyrate; MA, metabolic acidosis; Fe, iron; GRP 78, glucose-regulated protein 78; CotH, spore coat protein homolog. Illustration created by authors using BioRender.

Figure 1