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Pathogenesis of COVID-19-Associated Mucormycosis: An Updated Evidence-Based Review

Rimjhim Kanaujia[1] · Priya Sreenivasan[1] · Shivaprakash M. Rudramurthy[2]

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Abstract

Purpose of Review The current review gives a proper understanding of the various dynamics of COVID-associated mucormycosis (CAM). We provide insight into the agent and recent host-related factors that contributed to CAM. Also, we have discussed various environmental-related factors like fungal spore burden that could have contributed to the pathogenesis of CAM. This review also summarizes the main components of pathogenesis under three primary headings: the immunomodulatory effect of the virus, the involvement of underlying comorbidities conditions in the host, and the numerous treatment-related modalities used during COVID-19 treatment.

Recent Findings The risk factors for CAM continue to evolve with the development of COVID infection. A sudden rise in CAM cases was observed in countries including India. Along with *Rhizopus arrhizus*, the rise of other species like *Rhizopus homothallicus* and *Rhizopus microsporus* was observed. The virus along with underlying conditions like hyperglycemia, uncontrolled diabetes mellitus, diabetic ketoacidosis, and dysregulated iron metabolism with hyperferritinemia predisposes to CAM. Also, non-judicious and high-dose use of corticosteroids along with interleukins inhibitors (IL-1 and IL-6), and tocilizumab, contributed to a high rise in the cases of CAM. No link was found between the upsurge in CAM cases with the cow dung cake burning in India. Also, the possibility of nosocomial transmission was also raised, which was rejected as the majority of the patients remained at home during COVID-19 infection. Interestingly, in one study, the genetic similarity was observed between the strains isolated from the patient and the environment. Thus, the interplay of various factors like high spore count, uncontrolled diabetes, and the use of inappropriate steroids/IL inhibitors during the management of COVID-19 could have contributed to the alarming rise in cases of CAM.

Summary Mucorales are found ubiquitously in the environment. Understanding the pathogenesis and environmental factors like spore count and burden can provide insight into the development of CAM which is critical for optimal patient management. Also, COVID-19 management should include strict glycemic control and avoidance of any unnecessary medication.

Keywords Pathogenesis · SARS-CoV-2 · COVID-19 · Mucormycosis · Diabetes · Steroids

Introduction

The pandemic of SARS-CoV-2 (COVID-19) created a lot of havoc in the world claiming millions of lives. In addition to the COVID-19 pandemic, there has been an unexpected increase in the incidence of fungal infections among COVID-19-infected patients. Mucormycosis is one such serious angioinvasive fungal infection caused by a group of fungi, belonging to the order Mucorales. During the second wave of the pandemic, there was a sudden increase in the incidence of mucormycosis cases among COVID-19 patients, which eventually led to the coining of a new term "COVID-associated mucormycosis"(CAM) [1••]. In India, CAM was declared as a notifiable disease and many states

✉ Shivaprakash M. Rudramurthy
mrshivprakash@yahoo.com; mrshivprakash@gmail.com

Rimjhim Kanaujia
rim.pgimer@gmail.com

Priya Sreenivasan
priyambbs91@gmail.com

[1] Department of Medical Microbiology, Postgraduate Institute of Medical Education and Research PGIMER, Chandigarh, India

[2] Mycology Division, Department of Medical Microbiology, Postgraduate Institute of Medical Education and Research PGIMER, Room no. 211, Research Block A, Chandigarh, India

have even classified it as an epidemic. By July 2021, almost 40,000 cases of mucormycosis have been reported to the Government of India which is an underestimated value as many cases were not actually reported or properly diagnosed [2]. This momentous increase in CAM cases was recorded worldwide also [3–6]. The exact reason for this sudden upsurge in CAM cases is being studied by many experts, and many hypotheses have also been put forth regarding their pathogenesis. In addition to this, the role of fungal spores in the environment has been debated since the beginning. The alarming increase in CAM patients revealed numerous gaps in their pathophysiology. Many erroneous beliefs about CAM have been created because of the widespread outbreak of mucormycosis cases during the COVID pandemic. The agent, host, and environmental-related factors driving the significant spike of CAM over the COVID-19 timeframe require a comprehensive exploration. Therefore, the current review will provide an update on the different epidemiologic and environmental factors and COVID-19 treatment-related factors responsible for the upsurge of the CAM cases during the COVID-19 pandemic.

Global Burden of CAM Cases

With the onset of the COVID-19 pandemic, the Center for Disease Control, Atlanta released its first report on the rising incidence of various fungal infections such as aspergillosis, invasive candidiasis, and mucormycosis on December 1, 2020 [7]. Following that, there was an unprecedented rise in the number of individuals with COVID-19 who developed mucormycosis, leading to the development of a disease spectrum called COVID-associated mucormycosis. According to a 2018 study by Chander et al., the number of mucormycosis cases recorded in India is at a rate that is over 80 times higher than the global prevalence [8]. In the pre-COVID era, developed countries reported an overall incidence of 0.6 to 3 cases of mucormycosis per million population, whereas India recorded an incidence of almost 140 cases per million population [9]. In the COVID pandemic era, a meta-analysis of the global prevalence of CAM revealed a pool prevalence of 7 cases per 1000 patients, compared to the background data of 0.14 cases per 1000 patients in the pre-COVID time [10]. Another recent comprehensive analysis has shown that CAM accounts for almost 0.3% of co-infections in COVID-19 cases [11]. In a systematic review, Muthu et al. reported a higher number of cases (233) from India whereas only 45 cases were reported from the other parts of the world [12•]. Although the absolute number of cases was the highest in India, other countries like France and Germany reported higher cases in comparison to pre-COVID time [13, 14]. Another review of CAM from 18 countries has also shown that the majority of cases were from India (42 cases), while others were reported from the USA (8 cases), France (4 cases), Pakistan (5 cases), Iran (4 cases), and Mexico (4 cases) [15].

Between December 2019 and April 2021, India accounted for almost 70% of the global CAM cases. A multicentric case-control study of CAM cases from India conducted over 6 months (January to June 2021) revealed an overall prevalence rate of 0.27% (range, 0.05 to 0.57%) and in ICUs as 1.6% (range, 0.65 to 2.0%). In the same study, they confirmed that the overall CAM cases documented during the study period were higher than the previous year; however, the number of non-COVID-related mucormycosis patients remained constant [16••]. Prakash et al. have attributed several factors to the increased incidence of CAM cases in India, i.e., high Mucorales spore burden in tropical countries, endothelial dysfunction caused by the virus, hyperglycemia, and hyperferritinemia acting as sources for fungal growth [17].

Epidemiological Triad of CAM

Causative Agent

Mucormycosis is caused by different genera in the Mucorales family which includes *Rhizopus*, *Apophysomyces*, *Rhizomucor*, *Lichtheimia*, *Cunninghamella*, *Mucor*, and *Saksenaea. Rhizopus arrhizus* is the most commonly reported species globally as well as in India [9, 18]. In the pre-COVID era (2013–2015), a study of mucormycosis cases from tertiary care centers in South and North India revealed *Rhizopus arrhizus* (51.9%) as the most common agent, followed by *Rhizopus microsporus* (12.6%), *Apophysomyces variabilis* (9.2%), and *Rhizopus homothallicus* (2.5%) [19]. Interestingly, a few other species of *Rhizopus* like *Rhizopus homothallicus* and *Rhizopus microsporus* have been increasingly reported in recent times [19–23].

Host Factors

Traditional risk factors for mucormycosis are uncontrolled diabetes mellitus (DM) presenting with or without ketoacidosis and metabolic acidosis, corticosteroid treatment, neutropenia, bone marrow or organ transplantation, trauma, hematological malignancy, post tuberculosis, and in patients on hemodialysis patients with deferoxamine therapy [1••]. Few studies have even reported prolonged mechanical ventilation as a substantial risk factor in causing mucormycosis [16••].

The presence of a particular risk factor and the mode of transmission define the type of mucormycosis presentation. Inhalation is the primary mode of transmission, followed by either ingestion or traumatic inoculation of fungal

spores. In India, uncontrolled diabetes outnumbers the other risk factors which are often seen in developed nations, such as hematological malignancy and solid organ transplant. Recently emerging risk factors include viral pneumonia caused by SARS-CoV-2 [1••, 24].

Environmental Factors and Fungal Spore Burden in the Environment

Mucormycosis is an angioinvasive disease caused by the group of fungi of the order Mucorales, which are ubiquitous in the environment such as soil, decaying vegetation, and organic matter. Mucorales species are commonly found to inhabit soil, making them a major outdoor habitat. *Apophysomyces elegans* has been commonly reported in tropical regions [25]. *Rhizopus* spp., unlike *Apophysomyces*, thrive in high moisture conditions and have the propensity to settle on surfaces with liquid droplets in the air, which explains the absence of Mucorales spp. in air samples from interior habitats [26].

Cases of CAM were considerably higher in India when compared to other developing and developed countries, which could be attributable mostly to the high fungal spore burden in the environment. Because of the high spore burden, several subcontinent-specific practices such as burning cattle dung cakes (cultural and religious practices), stubble burning, and inhaling its fumes were hypothesized [27]. Kathirvel et al. investigated the number of Mucorales spores in the air before and after burning cattle dung cakes and reported no discernible difference in spore load. Furthermore, there was no noticeable difference in the percentage of Mucorales grown in families with and without cattle [28••, 29]. Thus, none of the preceding investigations found a link between cow dung cake burning and an increase in CAM cases in India [16••]. Also, the increase in CAM cases in countries where cow dung burning is not practiced alludes to other factors that may be responsible for the increase in CAM. Several other factors like India being the "Diabetes capital," a high fungal spore burden in the environment, and the usage of inappropriate medication during COVID-19, could also have contributed to an increase in CAM cases [29].

During the pre-pandemic era, few outbreaks of mucormycosis were observed in hospital settings due to contaminated linen and bandages, wooden tongue depressors, and stoma bags [30, 31]. An Indian study has also reported that 9% of the mucormycosis cases reported in their study were nosocomial [32]. The sudden increase in the number of CAM cases during the pandemic's second wave prompted attention to its nosocomial spread via hospital equipment and surfaces. To explore further, Biswal et al. conducted a multicentric investigation in various hospitals throughout India to determine the sources of nosocomial transmission and observed a very high fungal spore load inside the hospital setting in the ambient air and the AC vents. However, they did not find any source or hospital equipment contaminated with Mucorales as the source of the outbreak in their study [33•]. A prior study by Prakash et al. found a low fungal spore load both inside (0.88 to 1.72) and outside (0.73 to 8.60) the hospital environment throughout the year [34]. Despite a significant fungal load in the hospital environment, the majority of COVID-19 patients remained at home for symptomatic treatment. As a result, Ghosh et al. investigated the occurrence of Mucorales in the ambient air in these patients' residences. On analyzing the residence of 25 infected patients at home, they found a significantly high number of fungal spores in the patient's bedroom when compared to the other rooms (3.55 versus 1.5, $p = 0.003$) [35]. Interestingly, they found a genetic similarity between strains isolated from the patient's indoor environment and the clinical strains [35].

Pathogenesis of CAM

Immunomodulatory Effect of the Virus

The presence of a viral infection disrupts the overall immune function of the host, thereby increasing the risk of fungal infection [36]. In SARS-CoV-2 infection, the virus attaches to the ACE-2 (angiotensin-converting enzyme) receptor and causes impairment of ciliary motility, depressing innate immunity [1••]. Virus entry into the immune cells produces an increased proinflammatory response with high levels of IL-6 and TNF-α, ultimately leading to lymphopenia. Reduced dendritic cells along with defective neutrophils and monocytes result in a hyperinflammatory immune response. Another recent finding in the immune modulation of the SARS-CoV-2 virus is their ability to cause immune exhaustion [37]. This exhaustion is manifested by decreased levels of CD8 T cells and NK cells, along with an elevation in PD-1 and NKG2A, which has been found in COVID-19 patients, ultimately reducing antifungal immunity.

Role of Predisposing Comorbidities in the Host

Hyperglycemia

Hyperglycemia can be caused by various factors like diabetes mellitus, steroid usage, and stress-induced increased cortisol levels. Apart from this, the SARS-CoV-2 virus itself was found to damage the β cells of the pancreas directly causing insulin resistance, thereby ultimately resulting in increased blood glucose levels. This hyperglycemia causes upregulation of the expression levels of GRP78 (Glucose Regulator Protein 78), creating a favorable environment for fungal growth by increasing the production of CotH3 (spore

coating protein) [38] (Fig. 1). Furthermore, hyperglycemia causes dysregulation of immune response by impairing the overall activity of phagocytes and causes reduced antifungal immunity.

Diabetes Mellitus and Diabetic Ketoacidosis

Diabetes mellitus has been reported as a significant underlying risk factor in the development of mucormycosis in many descriptive and retrospective observational studies. Diabetic ketoacidosis is characterized by a reduction in the blood pH due to the presence of ketone bodies. As a result, the ability of transferrin to bind and transport iron is reduced, which further creates a favorable environment for fungal growth. In a study by Muthu et al., almost 80% of patients were diabetic compared to 45% in the control group, with diabetic ketoacidosis significantly higher in the CAM group (5.2% vs. 2.7%; $p = 0.0003$) [16••]. As mentioned before, the SARS-CoV-2 virus causes impairment of pancreatic beta-cell function and is found to precipitate diabetic ketoacidosis (DKA) [39]. This damage to the pancreatic β cells was found to be persisting even after recovery [40]. Thus, DKA could manifest even weeks or months after the recovery of the patient, supporting the late onset of acquiring CAM [4]. Diabetic mellitus increases the endothelial expression of a 78-kDa glucose-regulated protein (GRP78) and its ligand Cot H3 on *Rhizopus*, which is a co-facilitator for SARS-CoV-2 [1••] (Fig. 1). The experimental models have also confirmed the increased expression of GRP78 in the endothelial cells, contributing to an increased risk of acquiring mucormycosis. Muthu et al. have also revealed significantly higher serum levels of GRP78 among CAM cases when compared to COVID-19 controls suggesting an association with the virus [41].

Dysregulated Iron Metabolism and Hyperferritinemia

COVID-19 infection was found to cause dysregulation in the iron metabolism [42]. Hemoglobin production gets impaired as a result of virus interaction, resulting in hemolysis, and heme buildup. This leads to elevated serum ferritin, i.e., hyperferritinemia in response to inflammation [43, 44]. This excess intracellular free iron generates free radicals, which promote endothelial damage as well as facilitate fungal invasion [44] (Fig. 1). A study was conducted by Kumar and colleagues to investigate the serum iron indicators in COVID-19 patients with and without mucormycosis. CAM cases were found to have lower mean serum iron values and total iron-binding capacity (TIBC) compared to controls, confirming the dysregulation of iron metabolism in the pathogenesis of mucormycosis [45]. The low TIBC and iron may denote the poor binding of iron to transferrin and increased

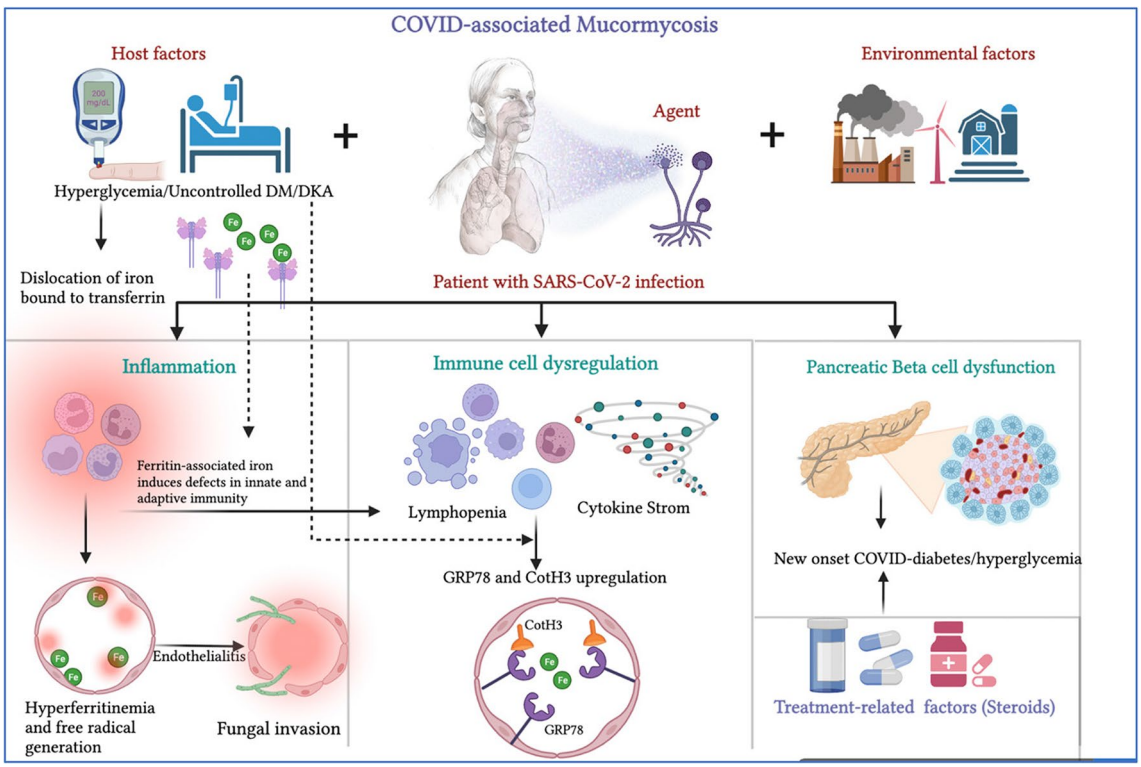

Fig. 1 An overview and interplay of the factors influencing the etiology of mucormycosis in SARS CoV-2 patients

iron availability for consumption of Mucorales during the development of CAM [45].

Role of COVID-19 Treatments

Corticosteroids

In the early stage of COVID-19 infection, the use of corticosteroids has been found to have an effective role [5]. The RECOVERY trial also revealed that the use of dexamethasone along with oxygen supplementation in COVID-19 hospitalized patients has resulted in a significant reduction in mortality [46]. While the use of steroids results in a reduced inflammatory response, improper administration may impair macrophage and neutrophil activity, by reducing their margination, chemotaxis, and phagocytosis. Apart from this, steroid use was found to disrupt glycemic control in patients, causing hyperglycemia (Fig. 1). Both these mechanisms increase the risk of acquiring fungal infection in COVID-19-infected patients by either favoring the fungal growth or disrupting the overall immunity of patients. Patients who received corticosteroids either in incorrect doses (6 mg/kg dexamethasone) or for longer duration (more than 10 days) or without the actual requirement of administration have been found to have a greater incidence of mucormycosis infections [4, 47]. Though steroid administration is itself considered a contributing factor to mucormycosis, a single-center study has shown that low doses of corticosteroids were found to have an enhanced recovery in 89% of ICU patients and also decreased the risk of acquiring mucormycosis. Another study has also reported that strict monitoring and administration of low doses of corticosteroids helped in achieving good glycemic control in 40% of their diabetic patients, and none of their patients developed mucormycosis [48].

Use of Interleukins Inhibitors (IL-1 and IL-6) and Tocilizumab for COVID-19

COVID-19 infection stimulates bronchial epithelial cells to produce IL-6, in a dose-dependent manner. To combat this and to prevent secondary infections, azithromycin was used by a few experts as it suppresses IL-6, which is crucial for antimicrobial defense, but clinical studies failed to prove better outcomes with azithromycin, and hence, the use was not routinely recommended [1••]. Another drug, tocilizumab, an FDA-approved medication, was taken alongside dexamethasone to reduce IL-6 levels in these individuals. Tocilizumab is a recombinant monoclonal antibody to the anti-IL-6 receptor. The drug which has been mainly used to manage the inflammation caused by COVID-19 substantially reduced the patient's overall immune response, which further increases the risk of acquiring mucormycosis in COVID-19 patients [49]. Zirpe et al. observed significantly higher odds of in-hospital mortality when tocilizumab was used in the management of COVID-19 infection [50]. However, a recent large Indian case-control study by Muthu et al. found no difference in the rate of tocilizumab treatment between patients with COVID-19 and with/without CAM [16••]. Though the use of immunomodulators is possibly hypothesized to be implicated in CAM pathogenesis, no current evidence identifies whether prior use of tocilizumab is associated with increased incidence of CAM [51].

Use of Industrial Oxygen, Oxygen/Face Mask, and Tap Water in Humidifiers

The second wave of the COVID-19 pandemic by the virulent strain of SARS-CoV-2 has caused severe disease in numerous patients, requiring oxygen and mechanical ventilation. According to Sen et al., 57% of the total patients in their study required oxygen assistance [47]. This unprecedented increase in oxygen demand led to the use of industrial oxygen in a few places instead of medical oxygen. Apart from the usage of industrial oxygen, increased patient load resulted in the use of non-sterile or tap water in oxygen humidifiers, which was proposed as a risk factor in the development of mucormycosis [52]. Industrial oxygen is not subjected to the same stringent cleaning and purity criteria as medical oxygen cylinders. Also, oxygen humidifiers are susceptible to bacterial and fungal infestation. However, these are merely a theory at this point, with no scientific support, and more research is needed to determine the significance of industrial oxygen consumption as a contributing factor in the rise in CAM cases.

Another factor attributed to the pathogenesis of CAM is face mask usage. However, as the fungal spores are ubiquitous and the exact etiology of the surge of CAM cases was not known, a hypothesis of potential contamination of face masks with Mucorales was proposed. Biswal et al. discovered that only 1.7% of 172 cotton masks collected in the study were found to be contaminated with Mucorales [33•]. This finding suggests that frequent mask usage is unlikely to be a contributing factor in mucormycosis outbreaks. However, the mere presence of an organism in the mask does not necessarily warrant infection, and more research is warranted in proving the association of face mask contamination as a risk factor for causing mucormycosis.

Conclusion

The unprecedented increase in CAM cases highlighted various areas of knowledge gaps that could be further explored and utilized in patient management. The pandemic-specific factors like the inappropriate use of steroids and various

medications like interleukin inhibitors have contributed to the development of CAM. Monitoring the glycemic index and the use of judicial therapy is essential in the prevention and management of CAM. However, further in vivo and in vitro studies are the need of the hour to establish the relationship between different factors which contributed to the pathogenesis of CAM.

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Declarations

Conflict of Interest The authors declare no competing interests.

Human and Animal Rights and Informed Consent This is a review article and does not involve any human or animal studies; hence, consent and ethical clearance are not required.

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- • Of importance
- •• Of major importance

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