REVIEW ARTICLE

THE MUCORMYCOSIS CRISIS: AN EPIDEMIC WITHIN A PANDEMIC

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ABSTRACT

With the second wave of COVID-19 in the April of 2021, the deadly mucormycosis outbreak surfaced in South Asia. Mucormycosis infection is an uncommon yet perilous angio-invasive fungal infection with a fatality rate of 54% globally. Immunocompromised COVID-19 patients with underlying comorbidities like diabetes mellitus and who were on prolonged steroid medications were the most vulnerable to develop this infection. Regionally, a highly disproportionate increase in COVID-19 associated mucormycosis (CAM) was observed. While there has been vigorous attention on the pathological risk factors, little attention has been paid to the environmental factors specific to different regions which may explain the grotesque increase in CAM cases in some regions while ordinary increase in the other. Recognizing the interplay between the two factors will aid epidemiologists in understanding the spread of the disease and help prevent future epidemics. This review analyzes the current literature on CAM to update clinicians on circumstances that lead to outbreak.

Keywords: Covid-19 Associated Mucormycosis, Mucormycosis, South Asia.

BACKGROUND

Along with the second wave of COVID-19 in April of 2021, the deadly mucormycosis surfaced both in Pakistan and India.[1] With the already collapsing healthcare systems due to the COVID-19 pandemic, both countries faced great challenges. Although, the situation in Pakistan was statistically better, it might possibly be due to insufficient surveys and an indeterminate number of unreported cases.[2,3]

Mucormycosis is an uncommon yet perilous, primarily angio-invasive fungal infection belonging to the order Mucorales and class Zygomycetes.[4] It is reported to be the third most common invasive mycosis infection after candidiasis and aspergillosis in immunocompromised patients.[5] Since most human infections from Zygomycetes class are caused by Mucorales, the terms mucormycosis and zygomycosis are often used synonymously. Mucorales are heat-resistant molds widely present in the environment, found in soil, decaying organic matter like rotten fruits and vegetables, compost piles, and animal excreta. However, its ubiquitous spread is still under study. It enters the body through ingestion, inhalation of spores or percutaneous route like inoculation into disrupted or abraded skin. The spores have no pathologic significance and are harmless in immunocompetent people.[6] Once inside the body of predisposed individuals, they germinate into hyphae and invades the blood vessels penetrating and eventually clogging them causing tissue necrosis that is characteristic black and dark in color and hence the name blank fungus is attributed to mucormycosis.[6,7] Depending upon the location of the invasion, six types of mucormycosis have been described, which are: (1) cutaneous, (2) pulmonary, (3) rhinocerberal, (4) gastrointestinal, (5) disseminated infection, and (6) uncommon presentations.[5,8] The most common occurring type is the rhinocerberal infection.[8]

It is a highly lethal infection and a fatality rate of 54% globally.[9]It has as rapid progression, a poor prognosis[8] and has been described as a 'time-sensitive' disease. If left untreated for merely six days, it can lead to a double-fold increase in the mortality rate. [10]The median time interval between the COVID-19 infection and the first appearance of the sign of mucormycosis was estimated to be fifteen days.[11]

MATERIAL AND METHODS

A comprehensive literature search was conducted from May to December 2021 using the following search terms: "COVID-19", "Covid-19 associated mucormycosis", "mucormycosis", and "South Asia" and BOOLEAN operators "AND" and "OR" were applied. The search terms were used as keywords and in combination as MeSH terms. We identified a total of (n=1,148) articles by searching databases, including PubMed (n=183), Scopus (n=207), and Google Scholar

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(n=758). After removing duplicates, screening and assessment for eligibility, (n=28) studies were included in the final review. These included original and review articles, brief communications, and published guidelines. In addition, a manual search of articles and other relevant studies was conducted and was included in the review that were missed in initial search. Articles in language other than English and articles regarding Apergillosis, Candidaisis and other opportunistic fungal infections were excluded.

DISCUSSION

Burden of CAM in Pakistan: Before the spread of COVID-19, Mucormycosis was mostly prevalent in immunocompromised patients with blood dyscrasias, malignancies and individuals who had undergone organ transplants. [7] While there is a paucity of data regarding the precise burden of overall fungal diseases in Pakistan, reports indicate high rates of mucormycosis infections even prior to the onset of the COVID-19 pandemic.[12] A study from 2017 estimated the rate of Mucormycosis infection in Pakistan to be around 14 per 100,000 (Non-Covid Associated Mucormycosis cases).[3] Nonetheless, a rapid increase in the prevalence of this infection was observed during the rise of COVID-19 cases in 2020-21, especially in India, where its prevalence was 80 times higher than the developed countries, estimated at 140 per million population.[7,13] Similarly, CAM rampantly became a cause of concern in different regions of Pakistan, as highlighted by the aforementioned studies. A multi-center, retrospective observational study conducted in Pakistan during the third wave of COVID-19 in 2021 aimed to observe the frequency and survival of CAM patients across three tertiary care hospitals in Punjab. Among the 43 documented cases of mucormycosis, 22 had a prior history of COVID-19 and diabetes mellitus was reported to be the most common co-morbid (88.4%).[14] Additionally, a case series highlighted the association between mucormycosis and COVID-19 infection in Pakistan, emphasizing the need for optimal glycemic management and early detection of mucormycosis to decrease morbidity and mortality associated with the disease.[15] These studies collectively underscore the significance of CAM in Pakistan and further emphasize the need for further research and surveillance to understand the specific epidemiological tendencies in the region.

Circumstance – what went down?: The circumstances that lead to a rise in COVID-19 associated mucormycosis (CAM) cases are multifactorial and may be attributed to many causes. When demands surpass the capacity of hospitals, reckless healthcare crisis becomes inevitable. Scarcity of medical equipment, supply shortages, burnout medical staff, and overcrowded hospitals and intensive care units due to the COVID -19 pandemic only exacerbated the situation. [16]

For instance, the high rise in mucormycosis infection could be associated with the inadequate supply of sterilized water for oxygen humidification in hospitals. Unsterilized water has a high possibility of being infected with fungal spores, which might be associated with an increased risk of mucormycosis transmission.[11] A study of three immunocompetent non-diabetic patients with high steroid intake, who were on supportive oxygen ventilation reported with rhino-cerbero-orbital mucormycosis (RCOM) which might be indicative of mucormycosis infection secondary to exposure of unsterilized water for oxygen humidification.[14]

Diabetes mellitus (DM) is an important underlying risk factor in the pathogenesis of mucormycosis.[17–19] Therefore, in order to understand the epidemiology of CAM, it is important to pay attention to DM cases regionally. According to the International Diabetes Federation, in 2021 India has the second-highest rate of DM cases (74.2 million) in the world after China (140.9 million), whereas Pakistan has the third highest cases (33 million) and an estimated 26.9% of adults in Pakistan are living with undiagnosed DM. [17]Moreover, the comparative prevalence rate for Pakistan in 2021 is estimated to be around 30.8%, highest in the world. A retrospective observational multi-centric analysis of 18 cases of RCOM illustrated a strong correlation between immunocompromised SARS-CoV-2 patients, diabetes mellitus, and steroid intake.[20] Another cross-sectional multi-centric study in Iran comprising of 15 cases of CAM depicted a high incidence of DM (87% cases), of which 46% were being treated with systemic corticosteroids, and 60% had nasal oxygen supplementation.[19]

Moreover, the administration of systemic corticosteroids for treating symptoms of COVID-19, as recommended by the World Health Organization (WHO), did mitigate the effects of COVID-19 symptomatically but also caused major drawback, i.e. the injudicious and unnecessary use of systemic corticosteroids. [21] A study in Pakistan revealed that the majority of the population in the second wave of COVID-19 consumed corticosteroids like dexamethasone as an early treatment of SARS-CoV-2 which resulted in delayed viral clearance.[22] This may also explain the CAM outbreak in the country following the second wave.[12]

Another plausible factor is that mucormycosis is complex to diagnose in its early stages and requires aggressive diagnostic strategies, posing great challenges for physicians.[2,8] It presents with non-specific symptoms like fever, headache, nasal and sinus congestion.[2,9]The diagnosis primarily lays on traditional methods like microscopic examination and culture tests for detection of mucorales which are time and labor intensive and require tissue biopsy specimens. The study of new, standardized, molecular and genetic based test like PCR assays is still being investigated. [8,23] In a developing country like Pakistan, unavailability of diagnostic laboratory facilities and anti-fungal susceptibility tests and lack of expertise in the area of antimicrobial examination imposed even greater challenge in the early identification of this disease.[2] As the CAM cases increased, cost of amphotericin B, the first-line antifungal drug for the treatment of mucormycosis infection also skyrocketed.[2,10] Research suggests that one infected person requires 20 vials of the liposomal amphotericin-B injection for treatment. Its non-availability further aggravated the situation.[21,24]

Regional Factors – A "missing link"?: Depending upon the individual perceptions and understanding, combined with a heavy influence of political norms and religious biases, different communities reacted differently to cope with the stresses of the COVID-19 pandemic, its treatment and prevention.[25–27] As described earlier, the two main factors that increase the risk of CAM were a great many DM cases and an unwarranted use of corticosteroids. However, the disproportionate increase of CAM cases in India as compared to other South Asian countries like Pakistan where DM is as prevalent[12] and where corticosteroid use was also reported to be high,[16] remains unclear. However, there have been hypotheses formulated which may explain the "missing link" in the vehement burden of CAM cases, and which may be attributed to a unique interplay of environmental and socio-cultural factors specific to India.[25] These are as follows: Firstly, use and burning of cow-excreta including dung and urine. This included burning cow dung cakes, drinking cow urine and other practices. States where cow slaughter was banned and use of cow excreta was less, like the state of Kerala showed a relatively smaller number of CAM cases as compared to areas like Tamil Nadu that faced highest load of CAM. Secondly, crowding in religious festivals including community bathing in holy river waters, for instance, the *Ganga* river. Thirdly, due to the increased COVID related deaths, burning of the corpses at the river embankments escalated in parallel. This significantly increased the water borne spread of mucroles.[25] In addition, converting and reconstructing hospitals into infectious disease control wards to in order to receive and a large inflow of COVID-19 patients is also related to increase risk of airborne spread of fungal spores.[24] On the other hand, in Pakistan these sociocultural factors were absent which may explain a comparatively small caseload of CAM in the country. Regionally, the major challenge in Pakistan was an underdeveloped, fragile health care system which was second to the widespread culture of denial amongst the general public and renunciation of the COVID-19 pandemic itself; dismissing it as a "Western conspiracy" or a "political game". This led to a jeopardized state of the COVID-19 standard operating procedure (SOP) and required informed public healthcare measures to be strictly implemented. [26,27]

Pathophysiological mechanism: Several pathophysiological mechanisms of SARS-CoV-2 increase the likelihood of an individual to opportunistic bacterial and fungal infections. Firstly, the cytokine storm syndrome in severe COVID-19 infection; a hyper-inflammatory state. SARS-CoV-2 is associated with increased production of pro-inflammatory cytokines, such as IL-6, IL-2 and TNF Alpha, that mediate inflammatory cascades resulting in cytokine burst and immune dysregulation. If not controlled, it can cause acute respiratory distress syndrome (ARDS), disseminated intravascular coagulation (DIC) or multiple organ failure.[28] Hence, to alleviate the effects, clinicians used immunosuppressive drugs which proved to be helpful. However, due to suppressed immune system, patients had a higher risk of catching opportunistic infections.[20]Additionally, there is increased likelihood of developing Insulin resistance and beta-cell dysfunction as SARS-CoV-2 can infect the islets cells of pancreas causing decreased production of insulin. In addition, increased levels of IL-6, as seen in COVID-19, are also linked to insulin resistance.[11]

Furthermore, COVID-19 is associated with the development of ketoacidosis, a potentially fatal metabolic complication, whether the patient has DM or not previously. Ketoacidosis or ketosis causes the pH of the blood to fall and become acidic. The acidic pH permits the germination of spores into filamentous hyphae structures that latch onto the blood vessels, blocks them and causing ischemia and tissue necrosis. This markedly hinders the chemotaxis of polymorphonuclear cells and also deters the phagocytic activity of the T-cells resulting in immune

dysregulation, therefore, increasing the susceptibility of an individual to acquiring opportunistic infections.[8,11]

Moreover, a recent study suggested a strong association between iron overload and CAM pathogenesis.[29] In fact, Severe COVID-19 infection is believed to be a hyper-ferretinemic state.[11] After entering the host, the virus attacks the hemoglobin in the RBCs causing the release of free iron in the circulation. To compensate for this increase, the production of ferritin; a protein that stores iron is stimulated. Excess ferritin levels cause death of the hepatocytes and subsequent release of iron from ferritin, leading to further increase of free iron in the blood.[30] In addition, acidosis and raised IL-6 levels associated with covid-19 are also linked to intracellular iron overload.[11,31] This is problematic because of two reasons. Firstly, excess free unbound iron plays a role in producing reactive oxygen species (ROS) and is linked to ferroptosis and hypercoagulative state observed in severe forms of COVID-19.[30] Secondly, pathogens in the host require a source of exogenous iron for growth and multiplication.[21] All these factors provide a perfect environment for mucormycosis to nourish and thrive in. Therapy with deferoxamine (DFO), an iron chelator used for the treatment of DKA and kidney failure patients who undergo routine dialysis is contraindicated in CAM and can reportedly cause a twofold risk of mucormycosis in immunocompromised COVID-19 patients.[3]

Additional factors include usage of certain drugs. For instance, overconsumption of steroid drugs like dexamethasone proved to be one of the leading causes as it is associated with lymphocytopenia, hyperglycemia and subsequently weakened immunity.[21] Moreover, the use of anti-IL-6 drug like Tocilizumab, prescribed for limiting the pro-inflammatory cytokine release in treating severe forms of COVID-19 infections like ARDS, also hampers the immune system rendering the body weak.[7,21] All these factors have been shown to ramp up the pathogenesis of CAM.

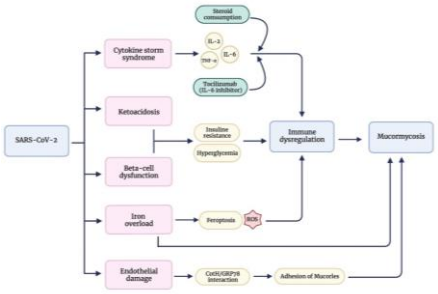

Figure-1: Illustrating the Pathophysiological Factors of Covid-19 Associated Mucormycosis (CAM).

Management and Treatment Approaches: Considering the fatal outcome of CAM and the rate with which the cases were surging, the European Confederation of Medical Mycology (ECMM) and the International Society for Human and Animal Mycology (ISHAM) composed standardized diagnostic criteria and a comprehensive management plan, including treatment approaches and preventive measures specifically devised for low- and middle-income countries.[32]

Global ECMM-MSG guidelines stated for CAM management are much alike the guidelines for non-COVID-19 mucormycosis patients.[31] For effective management of the disease, timely diagnosis using clinical, histopathological and radiological components remains as an indispensable factor.[7,32,33] Drug therapy with amphotericin B, and in case of its unavailability, treatment with other antifungal drugs have been stated clearly in the ECMM/ISHAM guidelines. One study has shown the survival rate in RCOM patients to be doubled (61%) if treatment with anti-fungal medication like amphotericin-B is started within the first twelve days of appearance of symptoms and it drops down to 33%, if started after thirteen days. Therefore, prompt anti-fungal treatment is crucial for the containment of the disease.[34] However, due to unavailability or intolerance, Posaconazole and Isavuconazole may also be used. But these are generally recommended as prophylaxis of mucormycosis infections.[35] In case of unavailability of Isavuconazole and posaconazole, Itrocanzole; another azole derivative may be recommended for mucormycosis management. However, its efficacy against Mucorales requires further trials and research.[32] Iron chelators as adjunct therapy have also been effective in patients with elevated serum iron levels.[7]

Moreover, timely surgical intervention for local containment of the infection is crucial. A recent study showed that CAM patients subjected to surgical therapy in adjunct to antifungal treatment had a survival rate of 64.96%.[7] Resection and debridement of the necrotic tissue for RCOM and affected lobe or lung in pulmonary mucormycosis are recommended. Surgical resection of RCOM requires a team of specialists like otolaryngologists, ophthalmologists and neurosurgeons.[32]

Therefore, a multidisciplinary approach involving microbiology and pathology specialists, critical care, ophthalmology, neurosurgery, and maxillofacial

surgery have proved to be imperative in decreasing the morbidity and mortality rate as well as evading possible complications.[4,21,32]

Preventative measures were also stated in the ECMM/ ISHAM guidelines. For instance, stringent checks on the glycemic control of diabetic patients, evidence-based use of systemic corticoids, use of surgical masks, and a high index of suspicion for signs of mucormycosis such as, facial ache, nasal blockage, swollen gums and loose teeth were suggested.[32]

CONCLUSION

Given the urgency of the circumstances, a global response was needed to curb the outbreak. This epidemic has made us learn that fungal infections cannot be ignored as a co- or super-infection in COVID-19 patients. Healthcare providers need to be vigilant and well aware, especially in high-risk patients. There is still limited research on the sequence of molecular mechanisms and pathogenesis of CAM. Moreover, the role of diagnostic imaging, medicinal and surgical interventions in the prognosis of the disease is under study. The solution demands a collaborative approach to better understand the epidemiology and prognostic importance of the disease, its multifaceted nature during the pandemic, and potential preventive methods to avoid future mucormycosis outbreaks.

CONFLICT OF INTEREST

None

AUTHOR CONTRIBUTION:

Asma Aamir: Study conception and design, Analysis and Interpretation of results

Faisal Hanif: Study conception and design, draft manuscript preparation

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