Mucormycosis - A Health Care Challenge in the COVID Era

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Abstract

The COVID pandemic has wreaked havoc worldwide with serious impact on the health, economy, education, and socialization. Many co-infections have resurfaced in the second wave of the pandemic, impacting clinical outcomes and mortality in these patients. Among the various post-covid complications, there has been a sudden spurt in the cases of COVID associated Mucormycosis. Mucormycosis is a deadly fungal infection caused by a fungi of the family mucoraecae. The incidence of Precovid Mucormycosis was confined to diabetics and immunocompromised patients and several cases have been reported in India, China and the Western world. There are numerous challenges in investigating this condition as the cause is multifactorial and cannot attributed to a single factor. There is an enormous increase in the use of disposable plastics in the form of personal protective equipments disturbing the homeostasis of the ecosystem. Biomedical waste management and training of health care professionals in maintaining a sterile hospital setting is the need of the hour. This paper will emphasize on the transition of Mucormycosis from the Precovid to post covid era, possible risk factors, challenges faced by the healthcare settings and biomedical waste management.

Keywords: COVID associated Mucormycosis; Pathogenesis; Hospital induced Mucormycosis Plastic pollution; Biomedical waste management

INTRODUCTION

Since the outbreak of Corona virus disease 19(COVID-19) in Wuhan, China, December 2019 caused by severe acute respiratory syndrome corona virus (SARS COV-2)[1], the disease has had diverse presentations in terms of symptoms, pathogenesis and treatment. COVID-19 patients present with a range of symptoms ranging from sore throat, dry cough, high grade fever, malaise, loss of taste and smell with systemic complications affecting the respiratory, cardiac and gastro intestinal system. The COVID-19 pandemic has wreaked havoc on health, economy, education, and socialization.[2] With the wide-spread start of vaccination drive worldwide we were in the phase of control of this pandemic. But, with the sudden surge in the COVID-19 cases the disease has rebounded with numerous post-covid complication, thus collapsing the entire health care system. In this article we will discuss a brief outline of the transition of Mucormycosis from the Precovid to post covid era, possible risk factors and the challenges faced by the healthcare settings.

Among the various post-covid complications, there has been a sudden spurt in cases of Mucormycosis. Mucormycosis is a deadly fungal infection caused by a fungi of the family mucoraecae. Pathogenic mucormycete genera include but are not limited to: Mucor, Rhizopus, Rhizomucor, Cunninghamella, Apophysomyces, Lichtheimia, Cokeromyces, Saksenaea [3]The onset of the disease is acute and rapidly progresses resulting in a fulminating and often fatal fungal infection. Diabetic and immunocompromised patients are most commonly susceptible to this deadly fungal infection.[4] The role of dental surgeons since the onset of pandemic has been eminent and with the surge of Mucormycosis, many patients are reporting with oral manifestations of this fungal infection.

The incidence of Mucormycosis in the Precovid era was low and mostly seen in diabetics. The epidemiology is difficult to determine because of its rarity. According to a review by Prakash *et al.*[5] there was a rise in the cases of Mucormycosis globally and most of the cases were from China and India and in patients with uncontrolled diabetes mellitus. The authors proposed that India had the highest burden of Mucormycosis with an estimated prevalence of 140 cases per million population and more than fifty percent of the patients were diabetic. Jeong *et al*.[6] in their meta -analysis reported a high disease burden of Mucormycosis, 34% in Europe, followed by Asia (31%) and North or South America (28%), Africa (3%), Australia and New Zealand (3%). However, maximum number of cases are from Asia and could be due to under reporting of cases. The most common predisposing underlying cause was seen in uncontrolled diabetes mellitus with ketoacidosis, immunocompromised patients, HIV infection, hematological malignancies, neutropenia, iron chelation therapy and patients on solid organ transplantation.[7]

Post-COVID there is an exponential increase in the prevalence of Mucormycosis. According to a global review by John *et al*.[8] more than two thirds of the cases were from India, (29/41,71%). In a multicentric retrospective hospital-based study COVID associated Mucormycosis was found in 187 (65.2%) of 287 Mucormycosis patients, and in 0.27 percent of hospitalized COVID-19 patients. During the research period, they noticed a 2.1-fold increase in Mucormycosis.[9]

There are numerous challenges in investigating Mucormycosis. The origin of the infection is multiple and cannot be linked to a single factor. The environmental sources include air, dust, soil and mostly invisible surfaces. Infections linked to construction, water leaks, insufficient air filtration, non-sterile medical supplies, deficient device reprocessing, dental procedures, contaminated linen, contaminated food and supplements, and other sources of mould can cause outbreaks among high-risk patients in healthcare settings. The other significant challenges include difficulty to study the origins of Mucormycosis infections in healthcare, in part because patients' medical histories might be extensive, with several exposures, and the incubation period for non-cutaneous Mucormycosis is unknown. Additionally, no standardized diagnostic criteria are available in the literature and there is a lack of Infection surveillance system for the general community.[10]

Pathogenesis of COVID associated Mucormycosis (CoV-M)

The risk factors in the development of CoV-M are listed in Table 1. Mucormycosis is believed to derive from inhalation of airborne organisms that invade the nasal, trachéal, or gastrointestinal mucosa.[11]According to evidence, SARS CoV-1 causes pancreatic islet damage, resulting in acute diabetes and DKA. Because there is a high expression of angiotensin-converting enzyme 2 receptors in pancreatic islets, as well as increased insulin resistance due to cytokine storm, this could describe the "diabetogenic state" in SARS CoV-2 infection.[12,13]

A change in iron metabolism occurs in severe COVID-19, in addition to hyperglycemia. Severe COVID-19 leads to a hyper-ferritinemic condition.[14] In normal patients' iron is tightly bound to proteins like transferrin. In diabetic keto acidosis and severe infection high serum iron is available due to proton mediated disassociation of iron from transferrin. High ferritin levels cause an overabundance of intracellular iron, which causes tissue damage by generating reactive oxygen species through the process of Fenton reaction. This reaction leads to generation of oxygen free radicals catalyzed by iron and causes cellular harm by oxidizing a wide range of cellular substrates. Reactive oxygen species (ROS) such as superoxide (O2•), hydrogen peroxide (H2O2), and hydroxyl radicals (OH•) are produced when iron (Fe2+) triggers the Fenton reaction. These reactions release harmful hydroxyl radicals, which can harm biological components like DNA, proteins, and lipids.[15.16]

Cytokines (IL-6) released during COVID infection promote ferritin production and downregulate iron export in response to severe infection and DKA, resulting in intracellular iron excess and worsening the problem. As a result of the tissue injury, free iron is released into the circulation.[14]The "endothelialitis" seen in severe

COVID-19 is another possible explanation for the link between COVID-19 and MCR. Patients who died of COVID-19 had more severe pulmonary vascular endothelial injury and new vessel growth than those who died of influenza A, according to autopsy studies. Early phases in MCR include endothelial adhesion and penetration.[17] The enthodelial receptor glucose-regulated protein (GRP 78) and the Mucorales adhesin spore coat protein homologs (CotH) are both induced by cademic and hyperglycemic conditions, generating a “perfect storm” for increased Mucorales adherence and penetration to the endothelium. GRP 78 has been proposed as one of the receptors involved in SARS-CoV-2 infection.[18]

SARS-CoV-2 infection is thought to affect CD4+ and CD8+ T-cells, which are crucial in the pathological process of COVID-19 infection. There is a drop in the absolute number of lymphocytes and T-cells in severe COVID-19 cases, which has been linked to the poorest outcomes. Mucorales-specific T-cells (CD4+ and CD8+) generate cytokines that destroy the fungal hyphae, such as interleukin (IL) 4, IL-10, IL-17, and interferon-gamma (IFN-). They concluded that such particular T-cells could be a helpful surrogate diagnostic sign of an invasive fungal disease because they were exclusively seen in patients with invasive mucormycosis.[19]

Hospital induced Mucormycosis

The origin of Mucormycosis is largely from the community but numerous studies have reported an increasing trend of nosocomial Mucormycosis from healthcare settings. According to a study the fungus thrives in hospitals where ventilator circuits and oxygen pipes are not properly sterilized.[5] Because severe covid patients require continuous oxygen therapy by high-flow oxygen delivered through nostrils, via a ventilator, Bilevel Positive Airway Pressure (BiPAP), non-rebreathing mask (NRM), and other devices, the risk of contracting an opportunistic infection rises. [20]Confirmed cases have been reported after use of contaminated linen, catheters, adhesive dressings, tongue depressors, wooden sticks and Osteotomy bags.[21]

Clinical presentation

Mucormycosis is classified into rhino-orbito-cerebral (ROCM), pulmonary, gastrointestinal, cutaneous, renal based on the regional anatomy affected. The disseminated forms include infection of the bones, heart, ear, parotid gland, uterus, urinary bladder, and lymph nodes.[6]Table 2- demonstrates the most common presenting symptoms in a patient with Mucormycosis. Mucormycosis is characterized by tissue necrosis as a result of angioinvasion and subsequent vascular thrombosis.[10,22] Because of its nonspecific symptoms and probable resemblance to bacterial osteomyelitis, trauma, and iatrogenic infections, oral signs of mucormycosis frequently include bone exposure and necrosis, which necessitates histological testing to establish the diagnosis.[22]

Factors involving disposing of plastic material used in patients

The pandemic has seen a sudden surge in the utility of single use plastics comprising of masks, personal protective equipments, gloves, medical test kits and disposable plastic containers. Improper disposal of the items has wreaked havoc on the world’s healthcare systems causing plastic pollution. Littering of these reusable items has led to rapid spread of the infection from contaminated surfaces. SARS-CoV-2 has been found to be more viable and stable for 2–3 days on plastics and stainless-steel surfaces than on cardboard, wood, banknotes, and copper, according to recent investigations. Healthcare professionals could utilize reusable surgical gowns instead of disposable single-use PPE, as suggested by the US FDA. Furthermore, healthcare providers may prioritise the usage of single PPE for various patients. Used personal protective equipment should be disposed of properly in well-labeled clinical waste containers, followed by recycling at certified biohazard waste treatment facilities, in order to solve the existing problem of environmental plastic pollution. The enormous plastic waste generated disturbs the marine and environmental ecosystem. The humans are also at a considerable risk due to the ingestion of seafood contaminated with particulate plastic.[23.24]

Medical waste management and sterilization[25]

The ongoing pandemic has emphasised the use of robust infection prevention and control practices in COVID-19 hospitals and other healthcare facilities.

a. Ventilation with focus on fresh air and natural ventilation wherever control systems with requisite air changes are not available.

b. Cleaning, disinfection and sanitation of the hospital environment and frequently touched surfaces, with recommended disinfectants like 1% sodium hypochlorite or 70% alcohol.

c. Safe water and food to prevent water or food borne diseases in hospital settings. Biodegradable items should be used.

d. The biomedical and domestic waste should be segregated and disposed.

e. Biomedical waste needs to be managed as per the central pollution control board (CPCB) guidelines. Separate colour coded bins with double layered bag and foot operated lids should be used for segregation of waste. The segregated waste can be incinerated or treated chemically and disposed.

f. Disposal of used PPEs5 - Waste masks and gloves in general households should be kept in paper bag for a minimum of 72 hours prior to disposal of the same as dry general solid waste after cutting the same to prevent reuse.

g. Most essential, only distilled water, not tap, filter, or RO water, should be used in the oxygen tubings and ventilators.

Management

Even in the presence of total ophthalmoplegia, early diagnosis, rapid beginning of systemic antifungal therapy, treatment of the underlying systemic illness, and forceful radical debridement of the sinuses are important to improving outcomes and orbital preservation. A multidisciplinary team comprising of ENT surgeons, ophthalmologist and dentists are required for treatment.[26,27] The medicine of choice is liposomal amphotericin B. As soon as the diagnosis is suspected, it should be started and given intravenously in a dose of 1.0–1.5 mg/kg/day in dextrose 5% solution.[28] Posaconazole and isavuconazole, among other triazoles, are widely used in the consolidation phase or as salvage therapy.[9] Since, severe arterial thrombosis and ischemic necrosis prohibit antifungal medications from reaching acceptable concentrations, medical treatment alone with antifungal drugs is ineffective. As a result, early debridement of infected and necrotic tissue, as well as drainage of diseased paranasal sinuses, is recommended. It also reduces the amount of fungal burden in the tissue.[28.29]

Conclusion

Early diagnosis is the key in preventing the severity and mortality of the condition. Training of health care professionals to change the water in flow meters and disinfecting oxygen tubing should be done on a regular basis in the hospitals. As the global burden of waste generation is increasing its advisable to use biodegradable materials and minimize the use of plastic to maintain homeostasis of the ecosystem. The patients should be motivated to maintain proper oral and nasal hygiene and monitor their blood sugar levels post covid treatment. They should be advised to use fresh masks daily and avoid contact with soil and manure and use gloves while working in such environment.

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