SARS-CoV-2 AND MUCORMYCOSIS: A REVIEW

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ABSTRACT

Mucormycosis is a rare and devastating disease caused by a ubiquitous fungus that belongs to the class Zygomycetes and order Mucorales.It is an opportunistic fungal infection which is most commonly seen in immunocompromised patients .The pandemic coronavirus disease 2019 (COVID-19) continues to be a significant problem worldwide.SARS-COV-2 is a cytokine storm syndrome that causes severe immunosuppression that might compromise the host response and increase the risk to develop opportunistic infections. There are several cases which have shown occurrence of Mucormycosis in patients who have a history of COVID -19. Therefore this review will highlight about the fungal infection Mucormycosis and its relation with COVID 19 disease.

Key words:SARS-CoV-2, Mucormycosis, Opportunistic infection
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INTRODUCTION

The pandemic disease coronavirus 2019 (COVID-19) still poses to be a significant problem worldwide.SARS-CoV-2 is responsible for lower respiratory infection and can cause Acute Respiratory Distress Syndromes (ARDS) [1]. The disease pattern of COVID-19 can range from mild to life-threatening pneumonia with associated bacterial and fungal coinfections[2].Due to the associated comorbidities (e.g., diabetes mellitus, chronic obstructive pulmonary disease) and immune compromised conditions (e.g. corticosteroid therapy, ventilation, intensive care unit stay), these patients are prone to develop severe opportunistic infections.[3-4].Several treatment options have been evaluated, none except systemic glucocorticoids have been shown to improve survival in COVID-19. However the usage of glucocorticoids can lead to secondary

bacterial or fungal infections. Moreover, the immune dysregulation caused by the virus and the use of concurrent immunomodulatory drugs such as tocilizumab could further increase the risk of infections in COVID-19 patients [5-6]. There are reports of the development of severe opportunistic infections such as oropharyngeal candidiasis, pneumocystis jiroveci pneumonia, pulmonary aspergillosis, bloodstream candida infections, etc., in patients affected with COVID-19 disease[4,7]**.** There are also few isolated case reports of rhino-orbital mucormycosis in COVID-19 patients[8-9]. Senet al. recently reported a series of six cases of COVID-19 disease with rhino-orbital mucormycosis[10] **.**Mucormycosis (previously called zygomycosis) is a rare and devastating disease caused by a ubiquitous fungus that belongs to the class Zygomycetes and order Mucorales[11].This review gives an insight about the relation between SARS-CoV-2 and mucormycosis.

MUCORMYCOSIS

The most common infections associated with immune compromised individuals are the fungal infections. They can be localized, systemic and invasive .Fungal infections can also have nosocomial etiology.

Phycomycosis or zygomycosis was first described in 1885 by Paltauf[12]and later coined as Mucormycosis in 1957 by Baker [13] for an aggressive infection caused by Rhizopus. The two orders, Mucorales and Entomophthorales belongs to the class Zygomycetes. These two orders produce dramatically different infections. Genera from the order Mucorales (Rhizopus, Mucor, Rhizomucor, Absidia, Apophy somyces, Cunninghamella and Saksenaea) cause an angioinvasive infection called mucormycosis[14].The nomenclature of Mucormycosis is suggested by anatomic site localization rather than by mycological classification. They can be classified according to the head and neck region as isolated nasal, rhino-orbital or rhino-orbital-cerebral Mucormycosis. Other accepted forms are pulmonary, disseminated, cutaneous, gastrointestinal and miscellaneous[15] The majority of clinical isolates accounts for the fungi of the genus Rhizopus. Mucoraceae are ubiquitous saprophytic fungi and are common inhabitants of decaying matter also found in bread, soil, air, dust and hospital ward rooms[16-18].The organisms are potent in the temperate climates[19]. The most common risk factors being diabetes mellitus, immunosuppressive therapy, leukaemia's and neutropenias[19]. Patients with neutrophil dysfunction, hematopoietic stem cell transplantation, diabetic ketoacidosis, iron-overload and HIV/AIDs are some identifiable risk factors. The mold usually gains entry into the host through the respiratory tract and exhibits a remarkable affinity for arteries and grows along internal elastic lamina causing thrombosis and infarction[20].The disease progresses fromthe nose and sinuses either directly or via vascular occlusion. Intracranial involvement also occurs by invasion through superior orbital fissure, ophthalmic vessels, cribriform plate[21], and carotid artery or possibly via a perineural route[22].

Diagnosis is classically dependent on clinical features & pathological findings. Imaging plays an important role in defining the extent of involvement [23]. Early establishment of the diagnosis and prompt surgical intervention, aids in controlling the extent and severity of the disease.

SARS-CoV-2 AND MUCORMYCOSIS

SARS-CoV-2 infection might alter the immune system by affecting T lymphocytes, particularly CD4+ and CD8+ T cells, which might be highly involved in the pathological process of COVID-19 infection[24]. The significant reduction of the absolute number of lymphocytes and specifically of T cells described in the most severe COVID-19 cases, isassociated with the worst outcome and could expose patients to a higher risk of developing opportunistic infections[25].

Mucormycosis is a fungal infection that might involve different organs, the most frequently affected of which are the lungs. [26-27]

Delay in diagnosis, an unbalanced immune system and a poor host response leads to high mortality rate in pulmonary localization. The treatment is also complex which includes a combination of antifungal therapy and a high-risk surgical intervention[28].Generally, mucormycosis affects immune compromised

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patients: as a matter of fact, a recent systematic review showed that solid organ transplantations and neutropenia, commonly reported in patients affected by haematological malignancies, were the only independent risk factors for pulmonary mucormycosis[29]. Furthermore, SARS-CoV-2 infection itself might trigger an alteration of the immune system [30].A complex interplay of factors, including pre-existing diseases, such as previous respiratory pathology, diabetes mellitus, , use of immunosuppressive therapy, the risk of hospital-acquired infections, and systemic immune alterations of COVID-19 infection itself may lead to secondary infections, which are increasingly being recognized in view of their impact on morbidity and mortality.[31]Koehler et al, in a recent retrospective study, analysed a cohort of patients admitted to ICU due to COVID-19 showing moderate to severe acute respiratory distress syndrome (ARDS) who developed invasive pulmonary aspergillosis as a consequence of the immune-paralysis related to SARS-CoV-2 infection [32].

Mucormycosis can involve nose, sinuses, orbit, central nervous system (CNS), lung (pulmonary), gastrointestinal tract (GIT), skin, jaw bones, joints, heart, kidney, and mediastinum (invasive type), but Rhino orbital cerebral Mucormycosis (ROCM) is the commonest variety seen in clinical practice world[33]. It should be noted that term ROCM refers to the entire spectrum ranging from limited sino-nasal disease (sino-nasal tissue invasion), limited rhino-orbital disease (progression to orbits) to rhino-orbital-cerebral disease (CNS involvement) .[34]The area of involvement may differ due to underlying conditions. For example, Rhino orbital cerebral Mucormycosis (ROCM) is frequently observed in association with uncontrolled diabetes, whereas pulmonary involvement is often observed in patients having neutropenia, bone marrow and organ transplant, and hematological malignancies, while GIT gets involved more in malnourished individuals.[35]

Recent reports indicates presence of Mucor in post covid patients between 15-17 days from day of covid report or even day 20 ,especially in patients who are diabetic or who have been given a high dose of steroids during the 14 day treatment or whose sugar levels have increased high during those 14 days . Patients show signs & symptoms of MUCOR infection such as Facial Pain, Para- aesthesia or complete anesthesia in Malar region, Pain, Para-aesthesia or complete anesthesia in the region of Alveolus &/or hard palate, Pain &/Swelling inthe Orbit (Eye) or in the peri-orbital Region, Chemosis, Fixed eyeballmovements, Diplopia, Loss of vision, Nasal Discharge, Blackish necrotic elementscoming out from the nose or sometimes oral cavity, Frontal Head ache. Patient may present with one, two, many or all the above mentioned symptoms.[35]

Patients suffering from severe viral pneumonia are at greater risk for developing ARDS that necessitates ICU admission, external respiratory support and corticosteroid therapy on background lung damage, conditions that worsen the overallclinical outcome. In a study on 432 patients with severe influenza pneumonia admitted to ICU, IPA (invasive pulmonary aspergillosis) was reported in 83 (19%) within a median of 3 days after admission. Further, the study reported 3-month mortality rates of 51% in patients with influenza/IPA (invasive pulmonary aspergillosis)co-infection versus 28% in those without IPA (invasive pulmonary aspergillosis) [36].

Early diagnosis and treatment is the key for treating this opportunistic infection.

The 1950 Smith and Krichner[37]criteria for the clinical diagnosis of mucormycosis are still considered to be gold standard and include:

- Black, necrotic turbinate's easily mistaken for dried, crusted blood,
- Blood-tinged nasal discharge and facial pain, both on the same side,
- Soft peri-orbital or peri-nasal swelling with discoloration and induration.
- Ptosis of the eyelid, proptosis of the eyeball and complete ophthalmoplegia
- Multiple cranial nerve palsies unrelated to documented lesions.

Advances in diagnosis have impacted the increasing reports on invasive mucormycosis in susceptible patients like those with diabetes ketoacidosis secondary to uncontrolled

diabetes, solid organ transplant (SOT), chronic respiratory diseases and corticosteroid therapy[36]. Since there are overlapping risk factors for developing IPA (invasive pulmonary aspergillosis) and pulmonary mucormycosis in patients with severe viral pneumonia,[38] it implies that pneumonia-associated mucormycosis is presumably under-diagnosed or under-reported. The prominent risk factors for sinosalmucormycosis are hyperglycaemia, use of IV dexamethasone and underlying lung pathology as highlighted by other studies[39-41].

Laboratory parameters such as CBC, ESR, FBS, PPBS, HbA1C, LFT, and RFT with electrolytes, CSF (if indicated) should be carried out .Nasal Endoscopic examination should be carried out for black necrotic eschar tissue.

Atypical chest imaging is seen at early phase of the disease or with extra pulmonary fungal infections. Therefore, surveillance of fungal pathogens is necessary for severely ill patients. This includes (i) etiological examination: direct microscopy andculture; (ii) histopathology; (iii) serology: antigen and antibody, (1,3)-b-D-glucan (BDG)[42] and galactomannan (GM) detection by serum are also need to be tested for suspicious patients, while bronchoalveolar lavage fluid (BALF) and tracheal aspirate (TA) sampling for culture and biomarker testing should be performed under well-protected conditions due to therisk of aerosol spreading and health care worker infections[43](iv) PCR-based methods: Real-time polymerase chain reaction (PCR) techniques and molecular identification can be performed to identify pathogens if necessary[44].After identifying the pathogen, the antifungal susceptibility testing (AST) can be performed to select sensitive antifungal drugs. If the AST cannot be carried out, it should be treated empirically. The European Confederation of Medical Mycology Mucormycosis Guidelines strongly suggest an early surgical treatment to remove the infected tissue (either through local debridement or complete resection) in addition to systemic antifungal treatment [45].

There are number of triggering factors that may precipitate mucormycosis in people with COVID-19 in relation to corticosteroids:[35]

(i) Presence of Diabetes mellitus with or without Diabetic ketoacidosis increases the risk of contracting mucormycosis and Diabetes mellitus is often associated with an increased severity of COVID-19,

(ii) Uncontrolled hyperglycemia and precipitation of Diabetes keto-acidosis is often observed due to corticosteroid intake. Thefertile media for mucor spores to germinate is low pH due to acidosis. Moreover, steroid use reduces the phagocytic activity of WBC (both first line and second line defense mechanism), causes impairment of bronchoalveolar macrophages migration, ingestion, and phagolysosome fusion, making a diabetic patient exceptionally vulnerable to mucormycosis.

(iii) COVID-19 often causes endothelialitis, endothelial damage, thrombosis, lymphopenia, and reduction in $CD4^+$ and $CD8^+$ level and thus predisposes to secondary or opportunistic fungal infection,

(iv) Free available iron is an ideal resource for mucormycosis. Hyperglycemia causes glycosylation of transferrin and ferritin, and reduces iron binding allowing increased free iron. Moreover, increase in cytokines in patients with COVID-19 especially interleukin-6, increases free iron by increasing ferritin levels due to increased synthesis and decreased iron transport. Furthermore, concomitant acidosis increases free iron by the same mechanism and additionally by reducing the ability of transferrin to chelate iron,

(v) High glucose, low pH, free iron, and ketones in presence of decreased phagocytic activity of WBC, enhances the growth of mucor. In addition, it enhances the expression of glucose-regulator protein 78 (GRP-78) of endothelium cells and fungal ligand spore coating homolog (CotH) protein, enabling angio-invasion, haematogenous dissemination and tissue necrosis [46]

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Therefore, it might be suggested that SARS-CoV-2 infection by itself can induce an immunosuppressive state that exposes the patient to the risk of developing opportunistic Infections, such as moulds. These kind of infections by themselves are associated with the worst outcome, especially when the immune system response does not improve. However, when the immune system recovers, opportunistic infections might be controlled [47].

CONCLUSION

SARS-CoV-2 infection is considered as a cytokine storm syndrome that causes severe immunosuppression that might compromise the host response and increase the risk to develop opportunistic infections, including those caused by moulds. Mucormycosis develops asan opportunistic infection in immunocompromised SARS-CoV-2 patients with uncontrolled diabetes and those who are on high dose of steroid thereby leading to higher risk of negative outcomes in the case of delayed diagnosis and inadequate treatment. The key to fight this fungal infection is early diagnosis and treatment.

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