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Coronavirus disease (COVID-19) Associated mucormycosis (CAM)

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Abstract. The currently prevalent COVID-19 infection, its line of treatment, resultant immunosuppression, and pre-existing comorbidities have made patients exposed to secondary infections including mucormycosis. Mucormycosis is a rare but in invasive fungal infection (IFI) due to several species of saprophytic fungi, occurring in patients with underlying co-morbidities which include diabetes mellitus, organ transplant, immunosuppressive corticosteroid therapy. The maxilla rarely undergoes necrosis due to its rich vascularity. Rare but not uncommon is the incidence of mucormycosis associated maxillary osteomyelitis occurring post COVID-19 infection. Fungal osteomyelitis is a life-threatening infection which may further spread from maxilla to the nose and paranasal sinuses within the orofacial region. It is an aggressive infection that needs to be addressed promptly to prevent fatal consequences.

Keywords: Mucormycosis, covid 19, fungal infection

1. Introduction

In such a testing time as the country is at war with COVID-19, the concern of post COVID-19 sepsis is emerging as a significant issue. Mucormycosis is a rare but serious infection that complicates the course of severe COVID-19. Subjects affected by COVID-19 infection with diabetes mellitus and multiple risk factors may be at a higher risk for developing mucormycosis. Diabetes is India's fastest-growing epidemic, with an estimated 77 million cases in the adult population. According to a recent cross-sectional survey conducted across all Indian states, 47 percent of Indians are uninformed of their diabetic status, and just a quarter of all diabetic patients attain sufficient glycemic control while on therapy [1]. While, several treatment modalities have been evaluated, none other than systemic glucocorticoids have been shown to improve survival in COVID-19. Unfortunately, Mucormycosis and Invasive pulmonary aspergillosis are few of the secondary opportunistic fungal infections owing to the widespread use of glucocorticoids [2]. Simultaneous glucocorticoid therapy probably increases the risk of mucormycosis. The venomous association between diabetes and the severity of SARS-CoV-2 infection has been repeatedly pointed out in various studies from across the world [3].

Mucormycosis (Zygomycosis, phycomycosis) is an angioinvasive infection due to filamentous fungi of the class Zygomycetes and the order Mucorales [4]. Mucorales are omnipresent moulds, amply found in the environment on decaying organic matter. Many studies from hospitals countrywide have

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revealed heavy mould spore counts even in hospital air due to predominantly hot, humid conditions in our tropical climate [5]. As a result, Mucormycosis, sometimes known as "rare mould" disease in western literature, affects roughly 140 people per million [6]. Clinical presentation is mostly found to be a delay in healing of a tooth extraction socket. Clinical features may include orbito-maxillary cellulitis, necrosis or eschar in the nasal cavity or on the palate with intermittent pus discharge, nasal congestion, halitosis, mostly asymptomatic but a few cases reported with dull pain. Opthalmoplegia and loss of vision suggests disease progression.

Epidural and subdural abscesses, as well as cavernous or sagittal sinus thrombosis, are all intracranial complications. It is linked to a high rate of mortality [7].

This being said, an early clinical diagnosis followed by a prompt treatment may surely increase the chances of survival.

2. Review of literature

With each passing day a myriad of manifestations and complications are being documented owing to this novel COVID-19 infection. Post COVID-19 sepsis occurs after severe-acute-respiratory-syndrome-coronavirus-2 (SARS-CoV-2) has had a frenzy in the human body. SARS-CoV-2 leads to an activation of the endothelium with thromboses in different parts of the body.

Goshua G, et al. 2020, in this single-centre cross-sectional study, hospitalised adult ($\geq$18 years) patients with laboratory-confirmed COVID-19 were identified in the medical intensive care unit (ICU) in hospital. Asymptomatic, non-hospitalised controls were recruited as a comparator group for biomarkers that did not have a reference range. The authors assessed markers of endothelial cell and platelet activation, including von Willebrand Factor (VWF) antigen, soluble thrombomodulin, soluble P-selectin, and soluble CD40 ligand, as well as coagulation factors, endogenous anticoagulants, and fibrinolytic enzymes. They compared the level of each marker in ICU patients, non-ICU patients, and controls, where applicable. The correlations between these laboratory results with clinical outcomes, including hospital discharge and mortality was done using Kaplan-Meier analysis which further was used to explore the association between biochemical markers and survival. It was interpretated, that the markers of endothelial cell and platelet activation were significantly elevated in ICU patients compared with non-ICU patients, including VWF antigen (mean 565% [SD 199] in ICU patients vs 278% [133] in non-ICU patients; $p < 0{\cdot}0001$) and soluble P-selectin (15·9 ng/mL [4·8] vs 11·2 ng/mL [3·1]; $p = 0{\cdot}0014$). VWF antigen concentrations were also elevated above the normal range in 16 (80%) of 20 non-ICU patients. It was found that the mortality was significantly correlated with VWF antigen and soluble thrombomodulin among all patients. In all patients, soluble thrombomodulin concentrations greater than 3·26 ng/mL were associated with lower rates of hospital discharge and lower likelihood of survival on Kaplan-Meier analysis. So, early identification of endotheliopathy and strategies to mitigate its progression might improve outcomes in COVID-19 [8].

Jung F (2020) proved that there was growing evidence that COVID-19 not only affects the lungs but beyond that the endothelial system also. Recent studies showed that this can lead to microcirculatory impairments and in consequence to functional disorders of all inner organs. The combination of endothelial dysfunction with a generalized inflammatory state and complement elements may together contribute to the overall pro-coagulative state described in COVID-19 patients leading to venular as well as to arteriolar occlusions [9].

Jung EM (2020) studied the contrast enhanced sonography (CEUS) which offered the possibility to analyze dynamic microcirculatory disturbances in real time dynamically without any risk for kidneys and thyroid gland even in severe progressing disease bedside. Based on severe COVID-19 infections, the first experiences with abdominal CEUS examinations were presented. In the stage of an imminent organ

failure with significantly reduced kidney and liver function, CEUS can be used to show a narrowing of the organ-supplying arteries, as well as a delayed capillary filling of vessels near the capsule, a regional reduced parenchymal perfusion or an inflammatory hyperemia with capillary hypercirculation. It is possible to quickly rule out organ infarction and to dynamically record the mesenteric arterial and venous blood flow [10].

Jung EM (2020) studied CEUS opens up new possibilities for bedside monitoring of pleural reactive inflammatory or peripheral thrombus embolism in severe cases of COVID-19 infection [11].

Colantuoni A et al. (2020) studied the spreading of Coronavirus (SARS-CoV-2) pandemic, known as COVID-19, had caused a great number of fatalities all around the World. The majority of patients affected by COVID-19 complained only slight symptoms: fatigue, myalgia or cough, but more than 15% of Chinese patients progressed into severe complications, with acute respiratory distress syndrome (ARDS), needing intensive treatment. They tried to summarize the data reported in the last months from several countries, highlighting that COVID-19 was characterized by cytokine storm (CS) and endothelial dysfunction in severely ill patients, where the progression of the disease was fast and fatal. Endothelial dysfunction was the fundamental mechanism triggering a pro-coagulant state, finally evolving into intravascular disseminated coagulation, causing embolization of several organs and consequent multiorgan failure (MOF) [12].

It leads to immune dysregulation caused by the virus and the use of concurrent immunomodulatory drugs such as tocilizumab [13, 14]. A dysregulated innate immune response, ciliary dysfunction, thrombo-inflammation, microvascular coagulation, cytokine storm and eventual immune exhaustion further facilitates secondary bacterial and fungal infections especially in critically ill patients. These highly susceptible hosts along with high fungal spore counts in the environment creates the perfect backdrop for mould infections.

Previously, only a few such incidental case reports had been published, but now there is a clear link between Covid-19 infection and increased fungal complications. Hanley et al. found a case of a 22-year-old male with disseminated mucormycosis affecting lymph nodes, heart, brain, and kidney in a postmortem analysis encompassing 10 patients with fatal COVID-19. Mehta and Pandey reported a single case of a 60-year-old male with rhino-orbital mucormycosis associated with Covid-19 in September 2020 [15]. In the same month, another such case report was published by Werthman-Ehrenreich [16].

White et al. studied 135 adults with Covid-19 infection, and reported an incidence of 26.7 % for invasive fungal infections [17]. Another study was conducted by Song et al. in April 2020 exhibiting the association between Covid-19 and invasive fungal sinusitis. This study concluded an increased risk of developing invasive fungal diseases was presented by a large number of patients affected by or recovered from Covid-19 and also gave a management algorithm for such cases [18]. In a recent review, 8 % of coronavirus- positive or recovered patients had secondary bacterial or fungal infections during hospital admission, with widespread use of broad-spectrum antibiotics and steroids [19].

Mucormycosis is a fungal disease associated with coronavirus disease 2019 (Covid-19) infected or recovered patients with a high mortality rate and increased incidence.

- The most common sinuses involved are the ethmoids followed by the maxillary sinus
- Diabetes mellitus, as well as coronavirus infection, are frequently associated with mucormycosis of the paranasal sinuses; uncontrolled diabetes increases the risk
- Intraorbital involvement is common, although intracranial involvement is uncommon.
- Extensive steroid and broad-spectrum antibiotic use for Covid-19 management may cause Mucormycosis

Oral lesions in patients with COVID-19 seem more likely to be induced by co-infections, immunity impairment, and adverse reactions instead of direct SARS-CoV-2 infection [21]. In routine maxillo-

facial practice, history of previous dental extractions leading to intra-oral exposed bone (maxillary necrosis) is generally diagnosed as osteomyelitis. Clinical features of fungal osteomyelitis are similar to bacterial osteomyelitis, exposed bone and pain with varying intensity. Patients have facial cellulites, anaesthesia, nasal discharge, necrotic turbinates, fever, headache, and lethargy in the early stages of the disease [20].

It was initially debatable whether someone taking immunosuppressants was more likely to contract COVID-19 or whether the immunosuppressive state caused more severe COVID-19 infection. However, immunosuppressants are still used unless the patients are at a higher risk of severe COVID-19 infection or are using high-dose corticosteroids8. COVID-19 infection, as far as we know, causes severe and long-lasting lymphopenia, which raises the risk of opportunistic infections.

It's also worth noting that 85 percent of COVID-19 patients had lymphopenia in their test results. This suggests that COVID-19 patients have a much-decreased absolute number of T lymphocytes, CD4+ T cells, and CD8+ T cells11. Because lymphocytes play such an important role in immunological homeostasis10, individuals with COVID-19 are particularly vulnerable to fungal co-infections. Furthermore, the SARS-CoV-2 virus's severe disease course damages lung tissues and alveolo-interstitial lesions, making the COVID-19 infected person vulnerable to invasive fungal infections, particularly those that are airborne or have a predominantly pulmonary entry.

Infections such as pneumocystis and mucormycosis are among them. Mucormycosis is an uncommon fungal infection that is frequently fatal. It is characterised by fungal hyphae invading the blood vessels, causing thrombosis and necrosis.

In COVID-19 patients, there has been an increase in mucormycosis coinfection, with numerous cases reported [21]. Radiologically, mucormycosis shows opacification of the sinus [22]. Therefore, a clinical suspicion of mucormycosis requires confirmation by radiological examination, preferably a CT scan of the maxilla and orbit, showing membrane or periosteal thickening and bony disruption, [22]. For fungal infection of the head and neck region and for visualizing bone destruction (bony changes) a CT scan is considered better than MRI [23].

The first choice is usually non-contrast computed tomography of the paranasal sinuses, followed by gadolinium-enhanced magnetic resonance imaging if intra-orbital or cerebral extension is suspected. The diagnosis is strongly suggested by focal bone erosions and extrasinus spread [24, 25]. Mucormycosis is determined by histology and/or culture of the organism from the affected locations, followed by identification of the isolate at the species level. A tissue sample that identifies the distinctive hyphae, a positive culture, or both can be used to provide a definite diagnosis of mucormycosis. The presence of the fungus is confirmed using Grocott's silver methenamine special staining procedure.

The best way to manage oral mucormycosis is early diagnosis, along with reversal of the underlying predisposing risk factors and systemic disorders, surgical debridement, and prompt administration of active antifungal agents [26, 27]. Surgical debridement of the infected area should be performed as soon as possible once the diagnosis is confirmed. Although surgery alone has not been demonstrated to be curative, an aggressive surgical approach has been shown to improve survival rates [28, 29]. Liposomal amphotericin B, at a dose of 5–10 mg/kg per day, is currently recommended for the treatment of mucormycosis. In the absence of central nervous system involvement, a dose of 5 mg/kg is suggested [30]. In cases refractory or intolerant to amphotericin therapy, posaconazole is considered a suitable alternative option [31].

3. Conclusion

We are learning more novel and long-term complications of the Covid-19 infection. Its association with invasive mucormycosis is perilious and must be given serious attention so as to be diagnosed at

the earliest. A high degree of clinical suspicion, Early diagnosis and timely management are customary to improve outcomes in mucormycosis. Uncontrolled diabetes and over-enthusiastic use of steroids are two of the significant factors aggravating the illness. A good prognosis and less fervent disease course can be achieved in cases of post-coronavirus mucormycosis by precise diagnosis, early surgical intervention and intravenous anti-fungal treatment for management. COVID-19 being a treacherous viral infection, clinicians should be keen-eyed to evaluate for mucormycosis in patients recovering from it. Further research is required to evaluate the potential link between these two infections.

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