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Pathology

MUCORMYCOSIS IN COVID ERA : A PATHOGENIC STORM

KEY WORDS: Covid 19, mucormycosis, steroids, black fungal infection

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ABSTRACT

Mucormycosis is a life-threatening infection caused by saprophytic fungi belonging to the genera Mucor, Rhizopus and Absidia which belong to the order Mucorales and class Zygomycetes._COVID-19 is associated with a significant incidence of secondary infections, both bacterial and fungal probably due to immune dysregulation. The judicious use of steroids/monoclonal antibodies/broad-spectrum antibiotics as part of treatment against COVID-19 has lead to the development/exacerbation of opportunistic infections. The use of therapeutic agents should be monitored to achieve a therapeutic effect at the lowest dose and shortest durations. The recent surge in cases of COVID-19 in India during the second wave of the pandemic had been associated with increased reporting of invasive mucormycosis post COVID-19, and are continuously being reported to be rising, popularly known as black fungal infection. In this review, we describe the important risk factors, clinical presentations, histopathology and outcome of mucormycosis in patients infected with SARS-CoV-2._Clinicians should be aware of the possibility of invasive secondary fungal infections in patients with COVID-19 infection and should enable early diagnosis and treatment with the subsequent reduction of mortality and morbidity.

INTRODUCTION

Rhinocerebral mucormycosis is a life-threatening infection caused by saprophytic fungi belonging to the genera Mucor, Rhizopus and Absidia. Covid-19 is a life-threatening, infectious disease in which decreased CD4 and CD8 positive cell counts, indicate susceptibility to fungal co-infections. Extensive use of steroids in Covid-19 management or associated with diabetes mellitus can also suppress immunity, allowing opportunistic fungal infections to colonise. Mucormycosis infection of the sinuses is a form of life-threatening invasive fungal sinusitis that typically affects immunocompromised individuals with an impaired neutrophilic response. 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 **(1)**

Risk factors (2)

Patients include those with

- Uncontrolled diabetes mellitus
- Neutropenia
- elevated free iron levels
- acquired immunodeficiency syndrome
- iatrogenic immunosuppression
- hematological malignancies
- stem cell transplants
- undergone organ transplantation
- Deferoxamine
- immunosuppressants
- Renal failure
- Protein calorie malnutrition

Other reasons could be the excess of uncontrolled conventional precautions. One such example is repeated steaming, which may distress the nasal tract's beneficial microbiome and virome. Nasal microbial imbalance (dysbiosis) may suppress local immunity and thus may provide opportunity for fungal infection. During Covid-19, in an attempt to prevent/ameliorate viral infection, an increasing number of people have been taking Zn disproportionately through vitamins and other dietary supplements. It is evident that the Zn deprivation inhibits fungal growth in the body. Therefore, Zn-depletion-based approach could be used for mucormycosis. In addition, many patients that were receiving medical treatment and were not on oxygen therapy were infected and diagnosed with mucormycosis. Therefore, there seems no definite link between oxygen therapy and the susceptibility to infection. In addition, mucormycosis depends on climatic factors such as seasonal variation, humidity, and ambient temperature. **(3)**

Pathogenesis

Mucormycosis or zygomycosis, also called phycomycosis, initially described in 1885 by Paltauf, is an uncommon and aggressive fungal infection that usually affects patients with alteration of their immunological system **(4)**. It is a lethal fungal disease, with rhinocerebral presentation being its most common form. Although it has a low incidence rate, varying from 0.005 to 1.7 per million population, many cases have been seen recently, amounting to a significant increase in its incidence in the ongoing coronavirus pandemic. Mode of contamination occurs through the inhalation of fungal spores. Fungal spores, reach the nasal cavity and make way to paranasal sinuses, germination is favored by low oxygen concentration, high glucose, acidic medium and high iron levels. They germinate into hyphae. Due to the metabolic hypoxic conditions, the Polymorphonuclear cells are less effective at removing these hyphae. Hyphae invade the blood vessels and the surrounding tissue blocking the blood flow and leading to tissue infarction. The orbit is accessible through the thin lamina papyracea of the ethmoid bone, infratemporal fossa, inferior orbital fissure, or orbital apex. The cribriform plate of ethmoid, supraorbital fissure, and perineural invasion are potential gateways to intracranial extension. It is important that physicians should pay critical attention to the high probability of increased incidence of fungal infections in Covid-19 affected or recovered patients.

Host microbe interaction in Covid 19 associated mucormycosis

In response to any invading pathogen, well functioning immune system initiates 2 main cellular responses, which is referred to as the "call to arms" and the "call for reinforcements." The call to arms induces Type-1 interferons, which acts as a warning to neighboring cells that an active infection is taking place and prepares those cells to ward off the virus as it attempts to spread. The call for reinforcements relies on the transcription factor nuclear factor kappa B (NF-κB) to induce secreted proteins that have chemoattractant properties, which recruit cells of the innate and adaptive immune response, including T cells, B cells, monocytes, neutrophils and natural killer (NK) cells, to help neutralize the threat at the site of infection. SARS-CoV-2 is unique in that it induces NF-κB while blocking INF-1, allowing SARS-CoV-2 to

replicate uninhibited, without a call to arms, while continuing to call for reinforcements. A significant amount of immune infiltrate (immune cells and cytokines in fluid) is generated, as a result, with neutrophil infiltration being one of the more noteworthy pathologies of the SARS-CoV-2 infected. These infiltrates are proinflammatory in nature. And as they accumulate, they begin to act on their own inflammatory environment, which ultimately generates the "cytokine storm" that is associated with severe COVID-19. Finally, the combination of infiltrate and the blocked induction of interferon, which typically stops the virus from spreading and causing excess cell death, can lead to respiratory distress. Direct damage to airway epithelial cells and blockage of INF-1 pathways increase susceptibility to fungal invasion. **(5)**

Complications

Cavernous sinus thrombosis, sagittal sinus thrombosis, carotid occlusion, cerebral infarction, intracranial aneurysm/hemorrhage and cerebral abscesses are direct consequences.

Clinical presentations

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 ROCM (Rhino-orbital-cerebral) is the commonest variety seen in clinical practice world-wide **(6).** 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) . The area of involvement may differ due to underlying condition. The Covid-19 infection caused by the novel SARS-CoV-2 has been associated with a wide range of disease patterns, ranging from a mild cough to life-threatening pneumonia [13]. Like SARS-CoV and Middle East respiratory syndrome, SARS-CoV-2 is also responsible for lower respiratory tract infection and can cause acute respiratory distress syndrome.[17] Patients may have diffuse alveolar damage with severe inflammatory exudation. It has been seen that the coronavirus-positive or recovered patients had secondary bacterial or fungal infections during hospital admission, with widespread use of broad-spectrum antibiotics and steroids. Due to the angioinvasive nature of the disease, skull base osteomyelitis and bone involvement is usually not seen or seen only late in the disease. The involved bones showed expansion, sclerosis, erosions and irregular lytic destruction.

The 1950 Smith and Krichner (7) criteria for the clinical diagnosis of mucormycosis are still considered to be gold standard and include:

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

Histopathology and Microbial findings

Histopathology remains the gold standard for diagnosis. Mucor is broad non-septate hyphae, wider than Aspergillus species and branch irregularly. Angioinvasion is seen which causes thrombosis. There is marked inflammatory response which can be neutrophilic or granulomatous. Giant cell invasion, thrombosis and eosinophilic necrosis of the underlying tissue is the pathological hallmark of mucormycosis. They can be easily seen on haematoxylin and eosin sections (figure 1). Special stains with PAS (periodic acid Schiff) or GMS (Gomori methamine silver) can be used to highlight the organisms and allow a clearer assessment of the morphology. **(8)**

Microbiological identification of the hyphae is based on diameter, presence or absence of septa, branching angle (right or acute branching), and pigmentation, differentiates it from other fungal infections. **(9)**

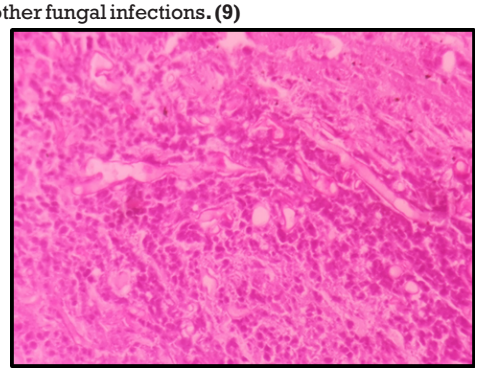

Figure 1 Broad, short hyphae of mucormycosis (H&E 40x)

Treatment and recommendations

One of the treatments for mucormycosis, amphotericin B, targets sterols, lipids found in cell membranes of both human and fungal cells. Ergosterol, a component of fungal cell membranes, is more sensitive to this antifungal medication than cholesterol, but administration of amphotericin B is limited by infusion-related toxicity that, once again, is likely the result of proinflammatory cytokine production. Furthermore, corticosteroid use during treatment with amphotericin B is known to cause metabolic imbalances like hypokalemia, further complicating medical intervention during CAM (covid associated mucormycosis). CAM has exposed a number of medical vulnerabilities that warrant further attention. For starters, few treatments exist for fungal diseases like mucormycosis.**(10)**

There is still much to learn from the pandemic and it is especially important to carefully monitor blood-glucose levels and thoroughly discuss any underlying medical conditions with patients before beginning corticosteroid use to treat COVID-19. All efforts should be made to maintain optimal hyperglycemia and only judicious evidence-based use of corticosteroids in patients with COVID-19 is recommended in order to reduce the burden of fatal mucormycosis. Over-zealous use of steroids in Covid 19 management can also suppress immunity, allowing opportunistic fungal infections to colonise which might aggravate the illness. Its association with invasive mucormycosis sinusitis is dangerous and must be given serious consideration. Histopathological examination must be needed for diagnosing it properly. If infected, early surgical intervention and intravenous anti-fungal treatment should be sought for management, as a good prognosis and less fulminant disease course can be achieved in cases of post-coronavirus mucormycosis.

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