Fungus in a Viral Land

Orbital Mucormycosis in Patients With COVID-19 Infection.

Sufia Imam¹, Dattatreya Mukherjee¹, Suriya N Harikrishnan¹, A.R Sinha²

1. Dept of Ophthalmology, First Affiliated Hospital of Jinan University, P.R China and International School, Jinan University, P.R China
2. Geomedi Teaching University, Georgia

This is a Preprint, Not Peer Reviewed

The coronavirus disease 2019(COVID-19) infection caused by the novel severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) may be associated with a wide range of disease patterns, ranging from mild to life-threatening pneumonia[1].

During the current pandemic of COVID-19, a myriad of manifestations and complications has emerged and are being reported frequently. We are discovering patients with COVID-19 are at increased risk of acute cardiac injury, arrhythmias, thromboembolic complications (pulmonary embolism and acute stroke), and secondary infections[2]. Recently, we have noticed that there is an increase in the incidence of invasive fungal infections in COVID-19 disease manifesting as orbital compartment syndrome, orbital cellulitis and rhino-orbital-cerebral mucormycosis. Several such cases have been reported during the course of COVID-19 disease or as a sequelae. In general mucormycosis infections are rare and opportunistic and are associated with high mortality ranging from 25-62%[3].

Mucormycosis is an invasive fungal infection caused by mold fungi of the genus *Mucor*, *Rhizopus*, *Rhizomucor* and *Absidia*, which are in the Mucorales order of the Zygomycetes class [4]. The most common type is *Rhizopus Oryzae* and approximately 60% of mucormycosis cases in humans; it is responsible for 90% of the rhino-orbital-cerebral form [5]. The pathogenesis of mucormycosis include killing of mucorales by mononuclear and polymorphonuclear phagocytes of normal hosts through generation of oxidative metabolites and defensins, hence neutropenic patients and those with dysfunctional phagocytes are susceptible to develop invasive mucormycosis[6,7]. A hallmark of mucormycosis infection is the presence of extensive angioinvasion with resultant vessel thrombosis, infarction and tissue necrosis[8].

In COVID-19 there is endothelial barrier disruption, dysfunctional alveolar-capillary oxygen transmission and impaired oxygen diffusion capacity[9]. Profound lymphopenia with reduced numbers of T lymphocytes, CD4+T, and CD8+T cells, may alter the immune response of COVID-19 patients enhancing the risk of invasive fungal infections[10].

We conducted a literature search online and read several published papers on 'mucormycosis post COVID-19 infection. Here we present to you the risk factors, clinical profile, investigations, treatment and prevention of this rare disease which is causing havoc during the COVID-19 pandemic.

Risk Factors: Preexisting morbidities like uncontrolled diabetes mellitus and lung disease, ventilator-associated pneumonia, neutropenia, elevated free iron levels, deferoxamine, hematological malignancies, stem cell transplants, and organ transplant patients on immunosuppressants, use of corticosteroids and tocilizumab, iatrogenic immunosuppressions, COVID-19 infection & its treatment causing immunosuppression.

Clinical Profile: fever, pain, redness, and periocular swelling, acute and progressive, drooping of eyelids, limitation of ocular movements, and painful loss of vision. The progression is usually rapid, an average of two days from the onset. Eyelid and periocular edema, complete ptosis, total ophthalmoplegia, proptosis and relative afferent pupillary defect, unilateral facial or orbital pain, headache, periocular swelling, double vision or diminution of vision, congestion with conjunctival edema and signs of exposure keratitis, chemosis, sinusitis, nasal discharge and neurological signs and symptoms if intracranial extension is present. The patients may exhibit one or more of the above mentioned signs and symptoms depending on the severity of disease.

Figure 1: Clinical picture of Orbital Mucormycosis with (a) left periocular edema, complete ptosis and (b) proptosis, conjunctival congestion, and severe chemosis.(Sen M, Lahane S, Lahane TP, Parekh R, Honavar SG. Mucor in a Viral Land: A Tale of Two Pathogens. Indian J Ophthalmol 2021;69:244-52.)

Figure 2: Axial scan of MRI orbit and brain of the same patient showing mild proptosis of the left eye, diffusion involvement of the ethmoid and sphenoid sinus, orbital apex (white arrow) and extension into the cavernous sinus.(Sen M, Lahane S, Lahane TP, Parekh R, Honavar SG. Mucor in a Viral Land: A Tale of Two Pathogens. Indian J Ophthalmol 2021;69:244-52.)

Investigations: Proven mucormycosis can be defined as histopathologic, cytopathologic or direct microscopic examination showing fungal hyphae in biopsy specimen with associated tissue damage, or a positive culture result. Serology- antigen and b-antibody, (1,3) D-Glucan and Galactomannan detection by serum, molecular identification (PCR). Magnetic resonance

imaging (MRI) of orbit, brain, and paranasal sinuses with or without computed tomography (CT) could be performed for assessing extent of the disease.

Figure 3(a-f) Axial, magnetic resonance imaging scans showing intra-orbital extension of mucormycosis. (Sharma S, Grover M, Bhargava S, Samdani S, Kataria T. Post coronavirus disease mucormycosis: a deadly addition to the pandemic spectrum. *J Laryngol Otol* 2021;1–6. <https://doi.org/10.1017/S0022215121000992>).

Figure 4: HPE of a patient showing aseptate hyphae with angioinvasion and Giemsa stain of the same showing black fungal elements in green background. (Mishra N et al. *Int J Otorhinolaryngol Head Neck Surg.* 2021 May;7(5):867-870).

- Prevention**
1. Avoid extensive use of steroids/monoclonal antibodies/broad-spectrum antibiotics during the treatment course of COVID-19 infection (may lead to the development/exacerbation of a preexisting fungal disease).
 2. Early identification of fungal co-infections may significantly reduce morbidity and mortality.
 3. Use of therapeutic agents should be monitored to achieve a therapeutic effect at the lowest dose for the shortest durations.
 4. Avoid Nosocomial Infections.

Treatment

Figure 4: Proposed guideline for surgical debridement and orbital exenteration for rhino-orbito-cerebral mucormycosis based on disease extent.(Sen M, Lahane S, Lahane TP, Parekh R, Honavar SG. Mucor in a Viral Land: A Tale of Two Pathogens. Indian J Ophthalmol 2021;69:244-52).

Conclusion: With the advent of COVID-19 Pandemic there has been turns and twists in terms of its pathophysiology, diagnosis, management, sequelae and complications[11].

As we learn more about COVID-19 and continue seeing more patients with this illness, we likely will continue seeing other unique presentations of other disease entities. Its association with invasive mucormycosis is dangerous and must be given serious consideration immediately. We also have to confirm whether this ‘Black Fungus’ is a previously undiagnosed mucor infection which may have been aggravated or it may have subsequently developed during the course of COVID-19 infections.

Clinical suspicion and early treatment with surgical debridement are key to preventing mortality and morbidity.

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