Case Series

A case series on post-covid deadly fungal infection: mucormycosis

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ABSTRACT
The prevailing pandemic situation by SARS-CoV-2 infection is not only worrisome by the disease per se but also for the accompanying opportunistic infection are in the rise especially in diabetic patients. We presented a case series of post-covid rhino orbital cerebral mucormycosis infection in diabetic patients resulting in high morbidity. The need to present this was to emphasis on the timely surgical and medical intervention needed to reduce morbidity and mortality by the infection. The study highlighted the importance of surgical intervention in the deadly infection.

Keywords: SARS-CoV-2, Mucormycosis, Steroids, Diabetes mellitus

INTRODUCTION
SARS-CoV-2 infection caused by coronavirus the reason behind the pandemic presents in varying patterns starting from mild to life threatening complication. The avid use of glucocorticoids in the treatment of COVID-19 infection has led to a deadly rise of infection by mucormycosis in many a patient. Mucormycosis is caused by fungi of Mucorales order belonging to the class of zygomycetes. The decline in innate immunity by COVID-19 infection and uncontrolled diabetes mellitus plays a major role in the angioinvasive fungal infection.

A total of 15 patients presented. 13 were male and 2 female. Out of the 15 patients, 10 of them have recovered from COVID-19 infection, 5 were covid positive when they presented to the department.

All the patients were monitored with complete blood profile, CRP, blood sugar levels. Diagnosis was based on KOH mount and histopathological examination of the specimen taken from nasal cavity.

All patients underwent surgical debridement of the sinuses and in 6 patients endoscopic orbital decompression and in 4 patients orbital exenteration was done. 12 patients improved clinically while 3 succumbed due to covid complications.

TREATMENT WITH SYSTEMIC ADMINISTRATION OF LIPOSOMAL AMPHOTERICIN B FOR A MINIMUM OF 4 WEEKS WAS DONE FOR ALL THE PATIENTS WITH REGULAR MONITORING OF RENAL PARAMETERS. 2 PATIENTS WERE STARTED ON INJECTION. ISONIAZID WHILE ONE PATIENT WAS STARTED ON Posaconazole postoperatively.

CASE SERIES
The prospective observational study was done in Dr. B. Nanavati hospital from December 2020 to May 2021. Patients presenting to ENT department with invasive fungal sinusitis were included in the study. All the patients included in the study were infected with COVID-19 infection and uncontrolled diabetes mellitus and were treated with steroids during management of COVID-19 illness.
Figure 1: Coronal T1 contrast enhanced image shows nonenhancement of inferior and middle turbinate represent black turbinate sign.

Figure 2: (a and b) A lobulated, partially enhancing T2 iso to hypointense soft tissue in the left ambient cisterns with resultant effacement of the pons; patchy T2 hyperintense areas, with restricted diffusion and foci of blooming are seen in the left brachium pontis extending into the pons suggestive of underlying cerebritis and evolving abscess.

Figure 3: Intra-op showing fungal sporangia in maxillary sinus.

Figure 4: Fungal sporangia removed from maxillary sinus.

Figure 5: Intra-op pics showing black eschar tissue in the right maxillary sinus.

Figure 6: Black turbinate.
In all patients the primary foci of infection was seen in ethmoid followed by maxillary. Sphenoid and frontal sinus involvement was less common.

HPE report showed broad thick aseptate hyphae morphologically resembling mucor, highlighted on PAS and GMS stains with non-invasive pattern while only one patient HPE report showed angioinvasive pattern. 13 out of 15 patients nasal biopsy sample sent intra operatively for KOH mount was positive for mucormycosis, the rest 2 patients demonstrated fungal growth in culture while being negative in KOH mount.

The number of patients for the site of involvement were as follows: nose (15), orbit (11), palate (3), complete vision loss (unilateral-6, bilateral-1); intracranial involvement (3).

For all patients MR imaging has been performed using GE Discovery MR 750 3.0 T scanner.

MRI protocol used is as follows: DWI, SWAN, axial T2 WI, axial Fiesta orbit; coronal STIR orbit, PNS, cavernous sinus; postcontrast T1 3D sequence, coronal orbit, PNS and cavernous sinus; coronal FLAIR.

Post contrast images were obtained after intravenous injection of gadopentetate dimeglumine (0.1 mmol/kg) after checking patient’s renal profile.

Image interpretation was performed by 3 radiologists to look for signal characteristics of mucormycosis, involvement of extra-sinosal sites and its complications. Imaging characteristics were maxillary and ethmoid sinus were most common sinus involved in our study. In the majority of patients multiple sinuses were involved. Bilateral involvement (60%) of the sinus was seen more rather than unilateral involvement (40%).

On MRI, the lesions were isointense to hypointense on T2W images in 3 cases (20%), hypointense in 7 cases (46%) and hyperintense like routine sinusitis in 5 cases (33%). In two cases, there was involvement of sphenoid sinus with extension into cavernous sinus and it was non enhancing on postcontrast T1 weighted images. In 5 cases there was extension from maxillary sinus into the pterygopalatine fossa and temporalis muscle with T2/STIR heterogenous hyperintensity with heterogenous post contrast enhancement. In 7 cases temporalis muscle showed STIR/T2 hyperintensity and 3 cases showed jaw and oral cavity extension, it was predominantly seen on STIR coronal images.

Contrast enhancement was categorised in 2 specific patterns (a) heterogenous enhancement in 9 patients (64%) and (b) peripheral rim-like enhancement with non-enhancing areas in 5 patients (35%). In one patient contrast was not administered due to deranged renal profile. There was characteristic black turbinate sign in 4 cases where there was nonenhancement of turbinate with
hypointensity on T2/STIR images relative to the other normal turbinates. This was suggestive infarction of the bone suggestive of invasive fungal sinusitis.

Five cases had intracranial extension with involvement of frontal and temporal lobe with areas of restricted diffusion suggestive of infarct which were acute to subacute stage. Two cases of intracranial invasion showed cerebritis and cerebral abscess and single case of invasive fungal sinusitis caused extensive vasculitis, infarct and multiple small haemorrhages related to it.

In 15 cases of mucormycosis, 8 patients had unilateral optic nerve involvement and only one case had bilateral optic nerve involvement. In these patients with optic nerve involvement, there was restricted diffusion with corresponding ADC hypointensity seen in 5 cases. There was retro-orbital fat stranding with extraocular muscles appears bulky in case of extraconal involvement. Mostly there was medial wall or floor of the orbit was involved which was seen on T1 weighted image as T1 hypointensity suggesting bone erosion.

### Table 1: Clinical details of the patients in case series.

<table>
<thead>
<tr>
<th>S. no.</th>
<th>Age/sex</th>
<th>Covid status</th>
<th>C/F</th>
<th>RF</th>
<th>Vision</th>
<th>Treatment</th>
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<td></td>
<td></td>
<td>R</td>
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* R-recovered; P-positive; RT-right; LT-left; ED-endoscopic debridement; EOD-endoscopic orbital decompression; OE-orbital exenteration; I-improved; E-expired; DM-diabetes mellitus; HTN-hypertension; IHD-ischemic heart disease; GCS-Glasgow coma scale; EO-external ophthalmoplegia; IO-internal ophthalmoplegia; RE-right eye; LE-left eye; Y-yes; P-paraesthesia; Pt-ptosis; NO-nasal obstruction; CK-cheek; MA-metabolic acidosis; S-swelli.
In our case series poorly controlled diabetes, prolonged usage of corticosteroids and the neutropenic status due to prolonged corticosteroid usage allowed proliferation of the fungus. The fungus adhered to the endothelial cells and damage resulting in angioinvasion, thrombosis and tissue necrosis and spread of infection to adjacent tissue.

**DISCUSSION**

Mucormycosis, also known as zygomycosis or phycomycosis is caused by *Rhizopus genera*. It is an angioinvasive fungal infection presenting with six clinical scenarios namely, cutaneous; rhino orbito cerebral (most common pattern); pulmonary; gastrointestinal; disseminated; uncommon forms like endocarditis, osteomyelitis, peritonitis and renal infection.3 Due to the ubiquitous nature of the fungi human infection occurred through inhalation of spores which stay as commensal in the nasal epithelium and the immunocompromised status predisposing to the infection. The predisposing factors for the fungal infection were poorly controlled diabetes, severe neutropenia, iron overload, prolonged usage of corticosteroids and malnourishment.

In our case series poorly controlled diabetes, prolonged use of steroids and the neutropenic status due to COVID-19 infection has led to infection by mucormycosis.

Pathogenesis of infection in rhinocerebral mucormycosis was the acidic pH of patient causes elevated serum free iron levels which led to rapid fungal growth and the neutropenic nature due to prolonged corticosteroid usage allowed proliferation of the fungus. The fungus adhered to the endothelial cells and damage resulting in angioinvasion, thrombosis and tissue necrosis and spread of infection to adjacent tissue.

The clinical symptoms in rhino orbito cerebral mucormycosis patient was sinusitis, periorbital cellulitis, facial pain and numbness with conjunctival chemosis, visual disturbances and neighbouring structures involvement like loss of extraocular muscle movement, pterygoid muscle and hard palate.
Investigations suggested are MRI brain and orbit being the gold standard, CT scan to detect bony erosion, KOH mount and fungal culture to confirm the diagnosis in aid with histopathology.

The mode of treatment in rhino cerebral mucormycosis was mainly surgical debridement with antifungal agents. The other adjunctive therapies suggested were iron chelators, hyperbaric oxygen as to improve the phagocytic property of the neutrophils and to inhibit the growth of fungi.

CONCLUSION

The deadly combination of COVID-19 infection and mucormycosis is dreadful warranting timely identification and intervention both surgical and medical to reduce the mortality and morbidity. Early diagnosis by nasal endoscopy prevents prolonged hospital stay and complications of the disease per se. Emphasis to be given for judicial administration of steroids in COVID-19 infection case to prevent the alarming rise of opportunistic infection and its sequelae.

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REFERENCES
