

A Case Series of Rhino-Orbital Mucormycosis in COVID-19 Patients

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Mucormycosis is caused by filamentous fungi of *Mucor*, *Rhizopus*, *Absidia*, *Apophysomyces*, *Saksenae* and *Cunninghumella* of the Mucorales order. Mucormycosis was first described by Paultauf A in 1885. Neutrophils play a key role in the host defence against mucormycosis. Ketoacidosis, hyperglycemia and hypoxia are excellent growth conditions for mucormycosis. Impairment of phagocytosis due to immunosuppression causes germination of spores into hyphae resulting in angio-invasion. Recently, the surge in mucormycosis is linked to the second wave of COVID-19 infection mostly due to uncontrolled diabetes in patients managed with steroids. India has emerged as being the mucormycosis capital in recent times. In this study report, we present the clinical findings and therapeutic outcomes of rhino-orbital mucormycosis in 3 male patients, age range between 45 - 75 years old all had diabetes mellitus and underwent treatment for COVID-19 pneumonia. All patients developed proptosis, sinusitis and decreased visual acuity with no light perception in the two patients with severe orbital involvement. Histopathological examination of tissue biopsy revealed typical Mucor hyphae. Systemic liposomal amphotericin B was initiated in all patients. The patients with limited ocular involvement received amphotericin B both intravenously and by local irrigation; one patient had complete recovery. All 3 patients underwent functional endoscopic sinus surgery (FESS) with orbital decompression and one patient needed orbital exenteration. One patient died after declining systemic treatment postoperatively. Early diagnosis and intervention with antifungal medication and surgical clearance of the disease may help avoid mutilating surgery like exenteration. Basic safety precautions like proper use of mask, single use of oxygen tube, using distilled water, hand washing and social distancing will go hand in hand to prevent the fulminant nature of the disease. Long term monitoring of patients is essential for favorable outcome.

Keywords: Mucormycosis; COVID-19; Diabetes Mellitus; FESS; TRAMB**Abbreviations**

DM: Diabetes Mellitus; FESS: Functional Endoscopic Sinus Surgery; TRAMB: Transcutaneous Retro-Bulbar Ampho-B; ROM: Restriction of Movements

Introduction

In recent times, the surge in mucormycosis is linked to the second wave of COVID-19 infection mostly due to uncontrolled diabetes mellitus in patients managed with steroids. Coronavirus disease (COVID-19) caused by severe acute respiratory syndrome

(SARS-COV-2) has been associated with a wide range of opportunistic bacterial and fungal infections. Several cases of Mucormycosis have been reported typically around 2 to 3 weeks of COVID-19 infection, even earlier by the end of the first week [1].

Mucormycosis is an uncommon life threatening invasive fungal infection that occurs mostly in diabetic and immune-compromised individuals, caused by filamentous fungi in the mucoraceae family. Mucorales spores germinate in COVID-19 patients due to hypoxia, high blood glucose level, steroid induced hyperglycemia, increased ferritin and decreased phagocytic mechanism in SARS-COV-2. Mucormycosis is an angio-invasive disease caused by mold fungi of the genus *Rhizopus*, *Mucor*, *Rhizomucor* and *Absidia* [2]. *Rhizopus oryzae* (60%) is the most common cause of mucormycosis.

Rhino-orbital infection occurs when fungal spores are inhaled and invade nasal mucosa. Sinusitis develops as the fungus spreads to paranasal sinuses; the most common form is rhino-cerebral (39%). This form may be divided into subtypes: rhino-nasal, rhino-orbital or rhino-orbito-cerebral. Orbital involvement occurs when the infection invades the orbital wall from paranasal sinuses. Symptoms may include pain, chemosis, vision loss, ophthalmoplegia and proptosis. Ophthalmoplegia arises from infection of the muscles, orbital space or when the third, fourth and sixth cranial nerves are affected. Peripheral seventh cranial nerve paresis or paralysis and hypoesthesia of the face are often observed. In this study, disease outcome in three COVID-19 patients with rhino-orbital mucormycosis are briefly discussed.

Cases Description

Case 1: A 48 years old male, known case of post COVID-19 pneumonia since 1 ½ month, diabetic for 4 years now. He came complaining of right sided facial pain with swelling around the right eye. On examination, diagnostic nasal endoscopy revealed mucopus with blackish necrotic material in right middle meatus. Ophthalmologic examination revealed right periorbital edema, right ptosis, conjunctival chemosis (Figure 1) and exposure keratitis inferiorly. Visual acuity was 3/60 in the right eye and 6/60 in the left eye with sluggish reaction of pupils to light and restriction of eye movements in all quadrants. Biopsy on KOH stain revealed aseptate/pauci branched broad hyaline hyphae suggestive of mucormycosis. MRI orbit and paranasal sinuses revealed enhancing inflammatory lesion in right maxillary and right ethmoid sinuses, and antero-inferior region of orbit. Right sided functional endoscopic sinus surgery and right orbital decompression was performed. A

necrotic fungal slough (Figure 2) was removed from the floor of the orbit. The patient was treated with inj. Liposomal amphotericin B 5 mg/kg, T. Posaconazole 300 mg BD on day 1, followed by OD dose from day 2 along with I.V. antibiotics and analgesics. TRAMB 1 ml of 3.5 mg/ml was given repeatedly of 3 doses. Endoscopic debridement of nasal cavity was performed thrice weekly. The patient got improved with regression of chemosis and uneventful postoperative condition. He was discharged after 25 days. Follow-up diagnostic nasal endoscopy showed healthy Sino-nasal mucosa and absence of necrotic material. Ophthalmologic examination showed improved ocular movements, decreased orbital edema (Figure 3) and right eye vision of 6/60 bed side, left eye 6/6.

Figure 1: Right eye periorbital edema with conjunctival chemosis.

Figure 2: Necrotic fungal slough removed from the right orbit.

Figure 3: Decreased chemosis and edema on 2nd postop day.

Case 2: A 72 years old male patient presented with complaints of complete loss of vision in the right eye, previously diagnosed to have COVID-19 pneumonia and subsequently underwent treatment for the underlying cause. The patient is diabetic for 7 yrs now. Seventeen days after COVID-19 treatment, the patient developed anosmia, nasal discharge, nasal bleeding with ptosis and diplopia with progressive loss of vision. Diagnostic nasal endoscopy showed black necrotic material in right maxillary sinus and middle meatus. Fungal culture 10% KOH mount revealed broad sparsely septate/aseptate hyphae with straight sporangiospores and spherical sporangia, rhizoids seen underneath sporangiospores suggestive of *Rhizopus* species. Ophthalmologic examination findings in the right eye were ptosis (Figure 4), mild proptosis and chemosis, pupil dilated 6 - 7 mm not reacting to direct light with ROM in all ranges. MRI PNS and orbit was suggestive of significant mucosal thickening with peripheral enhancement in both maxillary, right ethmoid, sphenoid and frontal sinuses. It also revealed mild thickening of right medial rectus with increased intensity and enhancement. MR Venography showed optic nerve infarct, superior ophthalmic vein appeared patent, subtle loss of void flow signal in right ophthalmic artery probably thrombosed. Right sided FESS and right orbital decompression was performed. A necrotic fungal slough (Figure 5) was removed from medial wall of the orbit. The patient was treated with inj. Liposomal amphotericin B 5 mg/kg, T. Posaconazole 300 mg BD on day 1, followed by OD dose from day 2 along with I.V. antibiotics and analgesics. TRAMB 1 ml of 3.5 mg/ml was given repeatedly of 4 doses. Vision could not be improved post operatively.

Follow-up MRI (Figure 6 and 7) revealed thrombosed right ophthalmic artery and operated cavity of paranasal sinuses.

Case 3: A 55 years old male patient presented with complaints of left eye swelling, previously treated for COVID-19 pneumonia, known diabetic for past 3 years on treatment. Hemoglobin level of 6g /dl, oxygen saturation level of 86% on room air. Initially, he was stabilized with I.V. ceftriaxone 1g bid, nasal oxygen at 6 lit/ min, one unit of packed cell volume of blood transfused. Diagnostic nasal endoscopy showed mucopus with necrotic material in left osteomeatal complex sent for KOH staining and revealed few aseptate,

Figure 4: Right eye ptosis with mild periorbital edema.

Figure 5: Black necrotic slough in right medial wall of the orbit and along the course of optic canal.

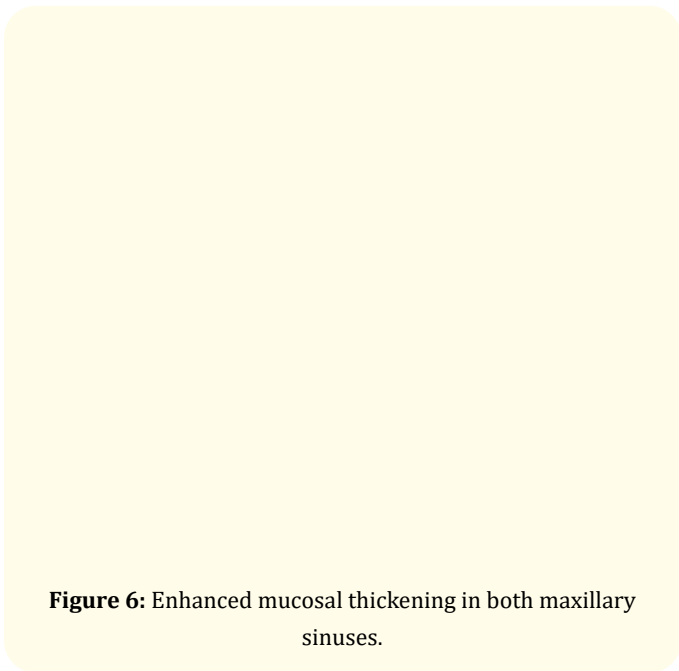


Figure 6: Enhanced mucosal thickening in both maxillary sinuses.

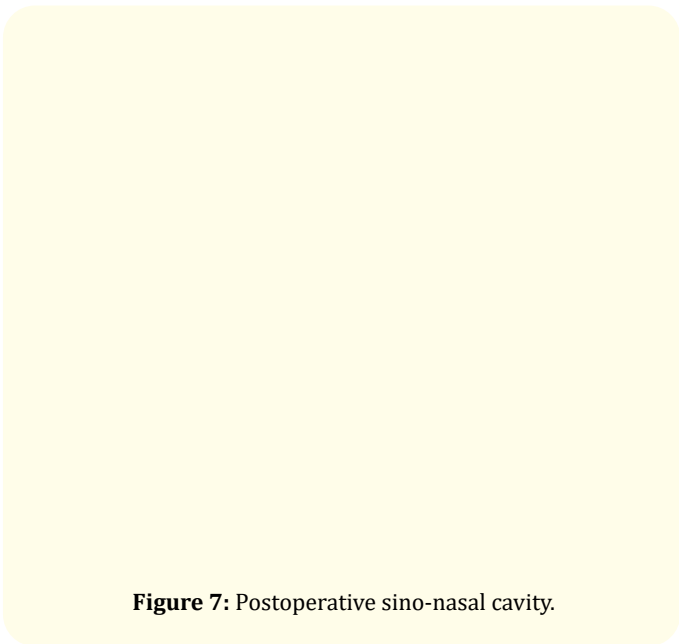


Figure 7: Postoperative sino-nasal cavity.

broad hyaline branched hyphae suggestive of mucormycosis. Ophthalmic findings are chemosis, proptosis and orbital cellulitis with loss of vision in left eye. MRI orbit and paranasal sinuses shows bilateral maxillary and ethmoido-sphenoidal sinusitis, left orbital cellulitis with peri-neuritis, proptosis of left eye ball. Multiple left sided flair neuro-parenchymal hyper-attenuation was noticed. Left

sided FESS and left orbital exenteration with maxillectomy was performed (Figure 8 and 9). The patient was treated with inj. Liposomal amphotericin B 5 mg/kg, T. Posaconazole 300 mg BD on day 1 followed by OD dose from day 2 along with I.V. antibiotics and analgesics. TRAMB 1 ml of 3.5 mg/ml was given repeatedly of 3 doses.

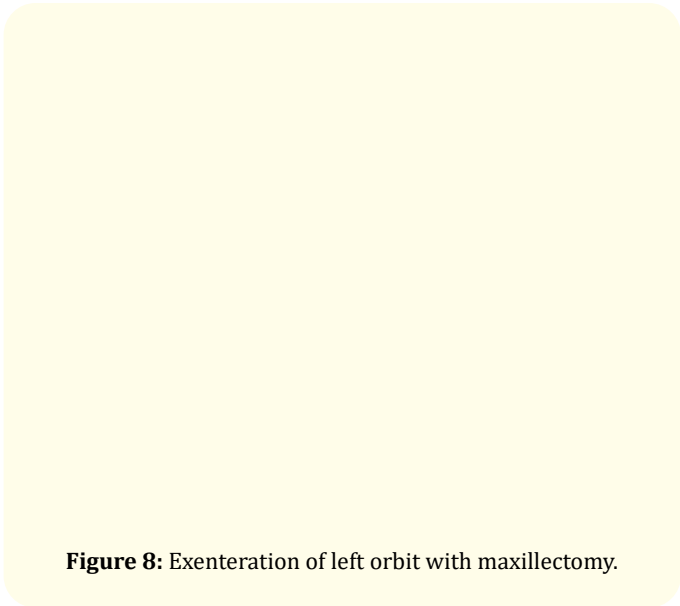


Figure 8: Exenteration of left orbit with maxillectomy.

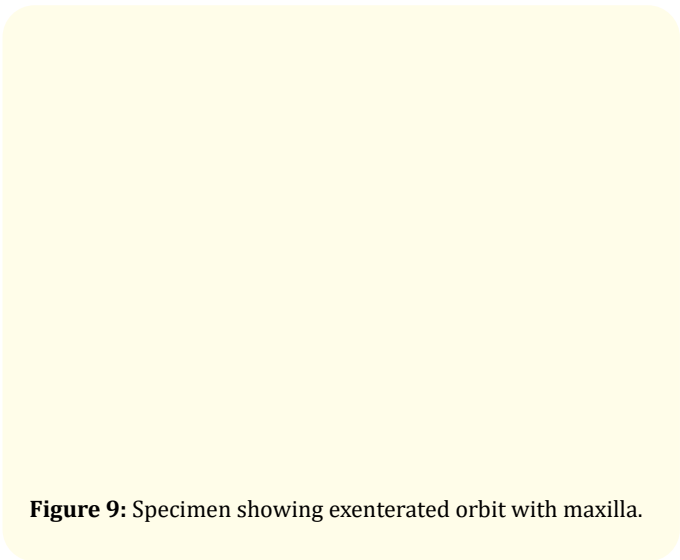


Figure 9: Specimen showing exenterated orbit with maxilla.

Results and Discussion

Mucormycosis occurs in several immunocompromised conditions like uncontrolled DM [3] with or without DKA, hematological and other malignancies, organ transplantation, prolonged

neutropenia, immunosuppressive and corticosteroid therapy, iron overload or hemochromatosis, severe burns, acquired immunodeficiency syndrome (AIDS). Mucormycosis can involve nose, sinuses, orbit, and central nervous system. Giant cell invasion, thrombosis and eosinophilic necrosis of the underlying tissue are the pathological hallmark of mucormycosis. Microbiological identification of the hyphae; based on diameter, presence or absence of septa, branching angle (right or acute branching) and pigmentation; differentiates it from other fungal infections.

Predisposing factors of mucormycosis in COVID-19 patients are as following:

- (i) DM is often associated with an increased severity of COVID-19 [3].
- (ii) Uncontrolled hyperglycemia due to corticosteroid intake.
- (iii) Low pH due to acidosis is a fertile media for mucor spores to germinate.
- (iv) COVID-19 often causes endothelial damage, thrombosis, lymphopenia, and reduction in CD4⁺ and CD8⁺ T-cell level [4], predisposing to opportunistic fungal infection.
- (v) Free available iron is an ideal resource for mucormycosis. Hyperglycemia, acidosis, increased cytokines interleukin-6 increase free iron by elevating ferritin levels due to increased synthesis, decreased iron transport and ability of transferrin to chelate iron.
- (vi) High glucose, low pH, free iron, and ketones in presence of decreased phagocytic activity of WBC, enhance the growth of mucor. In addition, they enhance the expression of glucose-regulator protein 78 (GRP-78) of endothelium cells and fungal ligand spore coating homolog (CoH) protein, enabling angio-invasion, hematogenous dissemination and tissue necrosis [5].

In our study, out of three different presentations, case 1 improved clinically after FESS and orbital decompression along with inj. Liposomal amphotericin B 5 mg/kg, T. posaconazole 300 mg, frequent endo-nasal debridement and nasal wash with deoxycholate amphotericin B. case 2 presented with right ophthalmic artery thrombosis and subsequent loss of vision, disease clearance was reached. Case 3 presentation was clinically deteriorated by the time he presented to ENT clinic. Salvage procedure was carried out by exenterating the left orbit with maxillectomy and FESS. TRAMB 1 ml of 3.5 mg/ml was given in all the three patients repeatedly of

3 to 4 doses. Goal of the surgery is to reduce the disease burden, allow better penetration of intravenous drugs, limit further spread of the disease and allow for histopathological and microbiological confirmation. Repeated surgical debridement may be required for local disease control.

Conclusion

COVID-19 related immunosuppression, prolonged use of high dose corticosteroids, poor glycemic control, use of other immunomodulatory medications (Tocilizumab, itolizumab), inappropriate use of broad spectrum antibiotics and antifungals, contaminated oxygen delivery devices or water used in humidifiers, prolonged use of unhygienic and contaminated masks, and increased use of industrial grade oxygen for medical purposes predispose to mucormycosis. Routine physical evaluation of a COVID-19 patient hospitalized with moderate to severe infection or diabetics with COVID-19 or those receiving systemic corticosteroids can include tests for vision, pupil, ocular motility, sinus tenderness and palatal eschar. A nasal swab for KOH mount and culture can be a bedside procedure. NK cell count in recovered COVID-19 patients is essential. Early diagnosis and intervention with antifungal medication and surgical clearance of the disease along with basic safety precautions like proper use of mask, hand washing and social distancing will go hand in hand to prevent the fulminant nature of the disease. Long term monitoring of patients is essential for favorable outcome.

Conflict of Interest

We hereby declare that we have no conflict of interest, related to this article "A case series of Rhino-orbital Mucormycosis in COVID-19 patients". Patients' photos have been published after obtaining verbal and documented consent.

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