Management and rehabilitation of rhino-orbito-cerebral mucormycosis in immuno-compromised patient- post COVID-19 – deterioration of deteriorated

Sri Lekha Rao	extsuperscript{1*}, Archana R Thool	extsuperscript{2}

ABSTRACT

A 27-year-old male with seropositive status came to ophthalmology OPD with complaints of swelling on medial side of left medial canthus and left lid edema since 2 weeks followed by diminution of vision in left eye since 8 days. History of complete loss of vision in left eye since 7 days. All necessary precautions were taken while examining and performing the surgical procedures. All necessary investigation was done. Patient was diagnosed with Mucormycosis infection which is more common among immunocompromised patients. Exenteration followed by prosthetic eye implantation was done along with necessary medical management. Follow-ups were done at regular intervals.

Keywords: Mucormycosis, COVID-19, immuno-compromised, diabetic mellitus, prosthetic implant

1. INTRODUCTION

Fungi and we live in the same world. Fungal species are incredibly common; according to recent estimates, there may be 5.1 million fungal species (Blackwell, 2011). Mucormycosis, also known as phycomycosis or zygomycosis, is an uncommon opportunistic fungal infection brought on by fungus from the Mucoraceae family and Mucorales order. Pautlauf described initially in 1885 (Viterbo et al., 2011). It is third most typical angio-invasive fungus infection after aspergillosis and candidiasis (Torres-Narbona et al., 2007). Immunocompromised individuals are affected mostly (Goel et al., 2009). Mucormycosis infection occurs in the compromised host as a result of impaired immunity, which leads to the fast proliferation and invasion of fungi into deeper tissues (Salisbury et al., 1997).

Rhino-orbito-cerebral mucormycosis is a lethal invasive fungal infection that accounts for 8.3–13% of all invasive fungal infections discovered in the
autopsy of haematological patients are rhino-orbito-cerebral mucormycosis, a fatal condition. Predisposing conditions include immunosuppressed children, diabetic ketoacidosis and haematological malignancies. Mucormycosis triad includes uncontrolled diabetes mellitus, periorbital infection and meningoencephalitis (Pahade et al., 2019; Saldanha et al., 2023).

2. CASE DESCRIPTION

A 27-year-old male came to the Ophthalmology OPD in May 2021 with complaints of swelling on medial side of left medial canthus and left lid edema since 2 weeks (Image 1). It was followed by diminution of vision in left eye since 8 days which is sudden in onset and gradually progressive in nature and painless type. Patient gives history of complete loss of vision in left eye within 7 days. It is associated with watering and discharge. Patient had no history of trauma or chemical injury. He also had complaints of left nasal obstruction, nasal congestion on and off and swelling over left side of cheek since 7 days. He had history of bleeding from nose of 2 to 3 episodes 6 days ago.

![Image 1](image1.png)

**Image 1** A- Preoperative photo with swelling over medial side of left eye. B– photo of post- exenteration surgery left eye

There was no h/o ear discharge, nasal discharge, loss of sensation over face, difficulty in swallowing and any other symptoms suggestive of covid. The patient is a newly diagnosed case of diabetes mellitus 1 month ago not on medication. He was diagnosed with COVID-19 infection in April 2021 (1 month ago), with HRCT score- 15/25. He was on treatment for the same as per COVID-19 guidelines. He was a diagnosed case of Hepatitis B virus infection. All necessary precautions were taken while examining the patient.

On Ophthalmological examination, right eye is within normal limits with 6/6 vision. No perception of light and no projection of rays present in left eye. In left eye, lid edema present with swelling on medial side of the eye. Pupil is fixed and non-reacting to light. Lens status was normal and posterior segment was within normal limits. Extraocular movements of left eye are restricted in all directions of gaze.

With all universal precautions, investigations were done. Random blood sugar is 509.8mg/dl. SGOT/AST is 40.9 U/L. LDH is 858.09 IU/L. CRP IS 46.41 mg/L. ABG report- blood gas values pCO$_2$ - 23.0 mmHg, pO$_2$ - 69.9 mmHg indicates ketoacidosis. IV fluids started, inj. Clindamycin 300mg 12 hourly, inj. Meropenem 1gm 8 hourly, tab. Posaconazole 400mg BD on day 1, followed by once a day. Patient was on inj. Insulin sliding scale 4 hourly. He is on eyedrop natamycin 6 times a day.

With all aseptic precautions and universal precaution 1.5mm linear incision on medial side of lower lid is given. Contents of the swelling were removed, cleaned with betadine solution. Dressing was done every day. Magnesium sulphate dressing done for first 3 days as the swelling present. Peribulbar injection of Amphotericin B (LIPOSOMAL) 3mg diluted with 1ml distilled water and 0.5ml 2% lignocaine in left eye was given for 7 days.
CECT PNS- ORBIT reveals mixed density areas noted partially opacifying bilateral maxillary sinus (left > right), frontal, ethmoid and sphenoid sinus with minimal enhancement on post contrast study. Attenuation of ethmoid septa and minimal extension into bilateral nasal cavity. Inflammatory changes noted in left orbital cavity predominantly involving medial aspect of orbital cavity. It is suggestive of pansinusitis likely fungal sinusitis (mucormycosis) and features of left orbital cellulitis. Axial CT section bone window showing defect in medial wall of left maxillary sinus and bilateral maxillary sinusitis (Image 2).

Image 2 CT scan image shows Axial CT section bone window showing defect in the medial wall of left maxillary sinus and bilateral maxillary sinusitis

CT brain plain suggestive non-enhancing hypodensity in left parafalcine (parasagittal) frontal lobe approximately measuring 3.6 x 1.7cm (AP x Trans). MRI Axial T2WI image showing hyperintensity in the extraconal soft tissue in the medial aspect of the left orbit, coronal section T1WI post contrast image shows enhancement of left extraconal soft tissue (Image 3). MRI Brain with orbit coronal T1WI post contrast image suggestive of peripherally enhancing lesions extending into frontal lobe (Image 4), infarct in left frontal lobe and head of caudate nucleus- left ACA territory.

Later he has undergone Functional Endoscopic Sinus Surgery. Samples are collected and sent for microbiology and histopathology. On KOH mount fungal elements seen. Growth suggestive of mucor species. Histopathology report suggestive of invasive fungal sinusitis. He was started on IV inj. Liposomal Amphotericin 5mg/kg body weight given. Inj. Liposomal amphotericin is diluted with 5% dextrose injection to a final concentration of 1 to 2 mg/ml prior to administration. Renal function tests were done before and after giving anti-fungal treatment. On day-5 patient has mild ptosis, semi-dilated fixed pupil and complete restriction of movements in left eye. Status post FESS, MRI ORBIT-PNS with BRAIN screening CONTRAST done suggestive of hyperintensity with post contrast enhancement noted at the orbital apex and orbital fissure.

Retro bulbar part of the optic nerve shows normal enhancement (Image 5). Intra conal fat appears normal. Bulky medial, inferior rectus and superior oblique muscles shows post contrast enhancement suggestive of involvement. There is increased enhancement along the floor and medial wall of the left orbit. Sections of brain show peripheral enhancing collection in cortical-subcortical region of left frontal minimal perilesional edema appearing hypointense onT1WI, hyperintense on T2WI with subtle leptomeninges and pachymeningeal enhancement s/o abscess another similar enhancing focus noted in the left basal ganglia.
The patient was then planned for lid sparing orbital exenteration in left eye under general anesthesia to curb the further spread of the infection. By taking all universal precautions surgery was done (Image 1). Intraoperatively medial wall defect was seen (Image 6). Histopathology slide showed fungal hyphae and necrosis (pink granular areas) suggestive of mucormycosis (Image 7). High dose broad spectrum antibiotics and anti-fungal medication were started and close monitoring is done. Following surgery, wound was healthy, no soakage, no discharge, sutures were in situ. Post-op MRI was done showing defect in left orbit (Image 8).

On postop day-7 infection was present at suture site in-spite of proper dressing every day. Infected area was incised and dressing done with antibiotic irrigation daily. Patient was discharged and was advised for regular dressing with local antibiotic application daily for 3 months. Adequate post – surgical care was taken to improve the overall immunity of the patient and blood
sugar level was monitored. Later he was advised for follow-up every 1 month. After 6 months of regular dressing and treatment healthy granulation tissue was seen. There was delayed healthy granulation tissue formation.

**Image 5** MRI image showing status post functional endoscopic sinus surgery - coronal post contrast TIWI

**Image 6** Intra-op photo showing medial wall defect of left eye
Image 7 Histopathology slide showing fungal hyphae and necrosis (pink granular areas) suggestive of mucormycosis

Image 8 Status post Exenteration left eye- MRI image - Axial T2WI showing defect in the left orbit

Patient came to ophthalmology OPD after 3 months. After proper examination he was advised for artificial prosthesis, where stepwise the socket is assessed for the size and then various models are prepared and fitted to the patient (Image 9). This was hand painted to match the other eye. Once the artificial eye is fabricated, we have explained how to wear, how to clean and how to care it. The best possible cosmetic restoration was done and patient was satisfied with the appearance. Now the patient has recovered and resumed his daily activities.
Timeline of the current episode
Patient came to ophthalmology department in May 2021.
He got admitted and reports were suggestive of pansinusitis and FESS was done in mid May.
Followed by exenteration surgery done in last week of May 2021
He came for follow-up after every 15 days for 2 months. Later he came for follow-up for every 1 month.
Infection was settled in orbital socket by the end of August 2021.
Wound was healthy by the end of November 2021.
Prosthetic implantation of eye was done in February 2022.

3. DISCUSSION
A global pandemic was caused by COVID-19, a disease linked to the SARS-CoV-2 virus, because of its rapid spread (Broughton et al., 2020). The degree of SARS-CoV2 infection-related symptoms ranges from mild to severe (Sabetian et al., 2021; Shahriarirad et al., 2020). Depending on the location, certain illnesses are more likely to be serious or fatal. Patients with COVID-19 may have increased levels of pro-inflammatory cytokines (such interleukin (IL)-2R, IL-6, IL-10 and tumour necrosis factor-alpha) as well as a compromised cell-mediated immune response that affects both CD4+ T cells and CD8+ T cells.

As a result, fungus coinfections are more likely to occur (Song et al., 2020). A combination of broad-spectrum antibiotics and corticosteroids is used to treat COVID-19 and acute respiratory failure (both of which are risk factors for invasive fungal disease) (Ranjbar et al., 2021). COVID-19 has been linked to immune dysregulation (Shafiekhani et al., 2021) and according to reports, COVID-19 patients run the danger of contracting invasive fungi including Pneumocystis jiroveci infection, invasive aspergillosis and candidiasis (Shafiekhani et al., 2021). However, the impact of medical treatment done during COVID-19 pandemic remains (Spellberg et al., 2009).

These fungi are common and can be found in soil and decomposing debris. Inhaling fungus spores or conidia is the most typical way that these fungi propagate. Inoculations into the skin, nasal mucosa or by ingestion as a result of trauma are the other mechanisms of transmission (Hargrove et al., 2006). The nose and Para nasal sinuses are the most often affected areas, but mucormycosis of the brain, lungs and skin has also been reported. These spores make their way into the blood vessels after entering the tissues and depositing there.
The lamina papyracea, infra-temporal fossa, inferior orbital fissure, superior orbital fissure or the orbital apex are the routes through which mucus travels from the nose and PNS to the orbit. Increased intracranial spread can result in headache, altered consciousness and even death. The preferred treatment is surgical debridement of tissues combined with intravenous amphotericin B1 mg/kg/day. Liposomal Amphotericin B, one of the newer Amphotericin B formulations, is effective in treating Mucormycosis. Azoles such as Isavuconazole and Posaconazole (oral suspension, delayed release tablets and infusion) are also employed as first-line therapy options (Cornely et al., 2019).

In the treatment of Mucormycosis, adjunct therapies should be taken into account. By giving neutrophils oxygen, hyperbaric oxygen destroys the fungus. Patients with diabetes need to have regular insulin and oral hypoglycemic drug intake monitored. Patients on immunosuppressant and steroids may also be told to cut back on their intake or dosage. Granulocyte colony stimulating factors can be used to boost immunity overall (Spellberg et al., 2005).

Clinical suspicion and early treatment are necessary for the condition to be cured. As a result, preventative medicine should be investigated if symptoms suggest mucormycosis and surgical debridement of the afflicted tissues and antifungal therapy are utilised to treat the condition. Amphotericin B is the medication of choice for primary treatment (Riley et al., 2016). Despite of early diagnosis and aggressive combined surgical and medical therapy, prognosis is poor (Roden et al., 2005). Cytological diagnosis, improvement of risk factors, systemic antifungal medication administered quickly and surgical debridement of contaminated tissue make up effective management.

4. CONCLUSION

Mucormycosis is a fungal infection which is not very common owing to its low virulence but become common in immunocompromised individuals suffering from long standing diabetes mellitus prior steroid therapy etc. Studying the patient’s status thoroughly and carrying out appropriate treatment is of paramount importance. With the help of aggressive resection technique and correct medical management it is possible to reduce the recurrence of mucormycosis. The main aim in reducing recurrence is by treating the underlying cause and regular follow ups to improve immunity.

Recommendations
Still with the continuing threat of variants of COVID-19 pandemic it is important to maintain good immunity and health. Necessary life style modifications should be done and proper diet should be maintained. It is a mutilating disease, which will affect the body in short duration, specifically in immune-compromised patients. Very poor prognosis is present in spite of aggressive medical and surgical management. It is apt to say in these situations that “prevention is better than cure”.

Acknowledgement
We would like to thank all the participants for their constant efforts and dedication towards the study.

Author Contribution
Dr B Srilekha has collected the information and prepared the manuscript which has been thoroughly reviewed and add added additional valid inputs by Dr Archana R Thool madam.

Informed Consent
Written and Oral informed consent was obtained from the individual participant included in the study. Additional informed consent was obtained from all individual participants whose information is included in the study.

Funding
This study has not received any external funding.

Conflict of interest
The authors declare that there is no conflict of interests.

Data and materials availability
All data sets collected during this study are available upon reasonable request from the corresponding author.
REFERENCES AND NOTES


