

Our Experience with Retrobulbar Amphotericin-B in Patients of Rhino-Orbital-Cerebral Mucormycosis (ROCM) at GMERS Gotri

Dr. Kamlesh Gendalbhai Damor¹, Dr. Ruju K. Upadhyaya², Dr. Hemali A. Patel³, Dr. Ashwini Sapre⁴

¹Senior Resident, Department of Ophthalmology GMERS Medical College, Gotri, Vadodara

²3rd Year Resident, Department of Ophthalmology, GMERS Medical College, Gotri, Vadodara

³Assistant Professor, Department of Ophthalmology, GMERS Medical College, Gotri, Vadodara

⁴HOD and Professor, Department of Ophthalmology, GMERS Medical College, Gotri, Vadodara
Corresponding Author Email address: [ashwinisapre71\[at\]gmail.com](mailto:ashwinisapre71[at]gmail.com)

Abstract: ***Purpose:** To evaluate ocular features in Rhino-Orbital-Cerebral Mucormycosis (ROCM) and to study outcome of retrobulbar injection Amphotericin-b in the patients of ROCM following COVID-19. **Methods:** 118 confirmed cases of ROCM following COVID-19 were analyzed retrospectively. **Results:** Out of 118 patients, 74 patients had disease in the nose and paranasal sinuses (PNS), 37 showed orbital involvement as well and 7 patients had severe disease involving the brain also. Out of 118 patients, 17 patients were given Retrobulbar Amphotericin-B injection of which 13 recovered well. 5 orbital exenterations were done, out of which one patient survived. **Conclusion:** Retrobulbar Amphotericin –B injection serves important role in preventing spread of fungus to the brain and improving mortality.*

Keywords: COVID-19, Rhino-Orbital-Cerebral Mucormycosis, Retrobulbar Amphotericin-B, exenteration

1. Introduction

The second wave of COVID-19 in India has presented challenge to the medical fraternity. Severe acute respiratory syndrome Coronavirus 2 (SARS-CoV-2) was found to be associated with systemic immune alterations including various bacterial and fungal infections.¹ Mucormycosis is commonly confined to the patients with altered immunity such as in transplant recipients, diabetics, patients with malignancies and patients on corticosteroid therapy. Uncontrolled diabetes is considered as the strongest risk factor for mucormycosis.^{2, 3} Mucormycosis is classified as rhino-orbital-cerebral, pulmonary, cutaneous, gastrointestinal and disseminated form based on the site of involvement. This article discusses the institutional experience of 118 cases of ROCM related to COVID-19 infection.

2. Methods

Ours is a Retrospective cohort study in which patients admitted for ROCM from April 2021 to August 2021 in GMERS medical college Gotri, Vadodara, Gujarat, India were taken into study.

Inclusion criteria: patients who are confirmed cases of ROCM based on Microbiological evidence for fungal elements of mucormycosis from biopsy sample were enrolled in the study.

Exclusion criteria: Non-consenting patients

Study procedure:

The assessment involves detailed history taking for clinical features and presentation of various symptoms, diabetic status, past history of COVID-19 & taking steroids treatment for COVID-19. Visual assessment was done with snellen's chart. Extraocular movements were checked in all gazes in all patients. For all patients ophthalmic examination of anterior segment was done with torch light and with slit lamp. Posterior segment for all patients was examined with Indirect binocular ophthalmoscopy after dilatation with Tropicamide 0.5 % eye drop.

Diagnosis

Diagnosis was made by MRI orbit+ paranasal sinus+ brain with gadolinium contrast in all suspected patients, diagnostic nasal endoscopy in all patients, tissue biopsy and histopathological examination during diagnostic nasal endoscopy or sinus debridement.

All patients with Microbiological evidence for fungal elements of mucormycosis from biopsy sample were given Intravenous Amphotericin-b after physician clearance and monitored for the same for continuation.

Criteria considered for Retrobulbar Amphotericin-B injection in RhinoOrbital-Cerebral Mucormycosis (ROCM) patients:

- 1) Patient consenting for the procedure
- 2) Positive findings on MRI showing either of these features:
 - Involvement of orbital floor, roof, medial or lateral wall
 - Involvement of orbital apex
 - Involvement of cavernous sinus

- Involvement of optic nerve/optic canal
 - Soft tissue inflammation of intraconal/extraconal compartment
 - Involvement of extraocular muscles
- 3) Clinical presentation with sudden visual loss

3. Results

Out of 118 patients there were 83 males and 35 females. The youngest patient was 17 years old and eldest one was 74 years old. Mean age was 49.25 (SD-11.26).

Table 1: Number of patient having predisposing factor

Total no. of patients	Number of patients having predisposing factor form ucor
118	112-Hyperglycemia
118	89 – Oxygen support
118	67 – steam inhalation

Of these 118 patients of mucormycosis, 74 patients had disease in the nose and paranasal sinuses (PNS) (rhino-mucormycosis), 37 showed orbital involvement as well (rhino-orbital mucormycosis) and 7 patients had severe disease involving the brain also (rhino-orbital-cerebral mucormycosis). Hence, a total of 44 patients (37+7) had orbital involvement. Among 118 patients of mucormycosis, 4 patients had positive perception of light (PL) only in affected eye, 5 patients had no perception of light with dilated non-reactive pupil (total ophthalmoplegia) in affected eye. One patient had bilateral involvement with No perception of light in both eyes on presentation. Remaining

patients had variable vision ranging from Hand movement to 6/6 on Snellen’s chart.

Out of 118 patients, 14 patients had total ophthalmoplegia in one eye on presentation. One patient had total ophthalmoplegia in both eyes on presentation. 7 patients had variable degree of muscle movement restriction in affected eye. While one patient had bilateral 6th nerve palsy leading to B/L lateral rectus restriction.

Out of 118 patients diagnosed with mucormycosis, 32 patients had one of following clinical features on presentation-lid edema, ptosis, proptosis, and conjunctival chemosis. 4 patients had presentation with cutaneous involvement in the form of black eschar.

Out of 118 patients, 71 patients had only mild to moderate sinusitis on MRI scan with contrast due to invasive fungal involvement. While 27 patients shown involvement of orbit on MRI scan. 4 patients had MRI finding suggestive of brain involvement.

Out of 118 patients diagnosed with mucormycosis, 17 patients were given Retrobulbar Amphotericin-B injection after satisfying criteria for the same. One patient refused for Retrobulbar Amphotericin-B injection after 2 doses. While one patient took discharge against medical advice after 2 doses of Retrobulbar Amphotericin-B injection. 13 patients were given total of 7 doses of Retrobulbar Amphotericin-B injection while 2 patients were given 9 doses of Retrobulbar Amphotericin-B injection due to recurrence of disease.

Table 2: Outcomes after retrobulbar amphotericin-B injection

Total No. of patients given 7 doses of Retrobulbar Amphotericin B for ocular mucormycosis	No. of patients with good recovery no recurrence of ocular mucormycosis	No. of patients needed two extra doses of Amphotericin B due to recurrence of ocular mucormycosis
15	13	2

Of 17 patients who were given Retrobulbar Amphotericin-B injection, 13 patients showed complete recovery of Extra ocular movements, clinical improvement in ptosis, conjunctival chemosis after completion of treatment.

These 13 patients showed no signs of recurrence of disease on follow-up. While 2 patients showed no clinical recovery of Extra ocular movements or ptosis after completion of 7 doses of Retrobulbar Amphotericin-B injection. 2 patients died after developing systemic complications such as thromboembolic events, cardiac arrest, and respiratory failure. Out of 17 patients who were started on Retrobulbar Amphotericin-B injection one patient had to be taken for orbital Exenteration surgery due to systemic progression of disease.

4. Discussion

Mucor and Rhizopus are the two most common species causing mucormycosis. They are found abundantly in the environment, commonly in hot and humid conditions. Mucormycosis has emerged as one of the life threatening complication of COVID-19 infection in India during second wave. Rhino-orbital-cerebral mucormycosis is a serious invasive fungal disease. It has a very high mortality rate

even with best possible treatment available. It acts by invading blood vessels and mycotic thrombosis causing infarction and ischemic necrosis of host tissue. 5 SARS-CoV-2 infection and post-COVID-19 causes altered immune response which leads to secondary bacterial and fungal infections. 6 Mucormycosis is highly associated with diabetic patients and its severity is more among uncontrolled diabetics. During COVID-19, prolonged corticosteroid treatment in patients especially with pre-existing conditions such as diabetes mellitus, organ transplant causes a susceptible host for invasive fungal infections like mucormycosis. 7 In India during second COVID-19 wave use of contaminated water with fungal spores for oxygen humidifier or use of contaminated and poor quality industrial oxygen during the shortfall of medical oxygen has been established as another indirect risk factor between COVID-19 and mucormycosis. 8

In our study, Out of 118 patients 112 were having uncontrolled diabetes during the time of admission in hospital. Eighty seven (87) patients had known history of diabetes, whereas 25 patients developed steroid-induced hyperglycemia. In our study 75.42% patients had taken Oxygen therapy during COVID-19 treatment while 56.7%

patients had taken steam inhalation at some period during COVID-19 infection.

The fungal spores reach sinuses through inhalation via nares which gets deposited in nasal mucosa. It reaches orbit through ethmoid bone, inferior orbital fissure, lamina papyracea or via orbital apex. The brain is involved when fungal infection directly involves cribriform plate, supraorbital fissure, or by perineural invasion and hematogenous spread.⁹ In our study, 74 patients had disease restricted to nose and paranasal sinuses (PNS), 37 showed orbital+ paranasal sinuses involvement and 7 patients had severe disease involving orbit+paranasal sinuses+brain.

Medical treatment of mucormycosis includes antifungal therapy and control of associated systemic diseases mainly diabetes. While surgical treatment includes debridement of necrotic and unhealthy tissues from nose, paranasal sinuses and other involved tissues. Exenteration was indicated when there was due risk of involvement of brain.¹⁰

In our study, all of 118 patients were treated with Intravenous Amphotericin-B injection after physician clearance. On discharge they were treated with oral Posaconazol for three months. While 14% patients were treated with Retrobulbar Amphotericin-B injection. 94% patients underwent extended endoscopic sinus surgery and debridement. While 4.2% patients underwent orbital exenteration.

In retrospective analysis, high mortality rate has been seen in patients who underwent orbital exenteration. In our study out of 5 patients who were treated with exenteration 4 patients died after surgery due to systemic complications, which is mortality rate of 80% of treated patients with exenteration.

In our study, 17 patients were treated with Retrobulbar Amphotericin B injection. Out of these 17 patients, 13 patients had complete recovery in terms of extraocular movements and clinical features which accounts for 76% recovery rate. While 2 had no clinical improvements which is 11% of treated with Retrobulbar Amphotericin-B injection. While 2 died due to systemic complications. One patient had to be taken for orbital exenteration surgery.

5. Conclusion

Retrobulbar Amphotericin-B injection serves important role in preventing spread of fungus to the brain and improving mortality. Role of Exenteration in improving mortality can be debatable further. Patients should be educated regarding sign and symptoms of mucormycosis in recovered COVID-19 cases. Follow up at regular interval in recovered patients should be done.

References

[1] Chen N, Zhou M, Dong X, et al. Epidemiological and clinical characteristics of 99 cases of 2019 novel coronavirus pneumonia in wuhan, china: A descriptive study. *Lancet*.2020; 395 (10223): 507-513.

- [2] John TM, Jacob CN, Kontoyiannis DP. When uncontrolled diabetes mellitus and severe COVID-19 converge: The perfect storm for mucormycosis. *J Fungai*.2021; 7 (4): 298.
- [3] Lim S, Bae JH, Kwon H-S, Nauck MA. COVID-19 and diabetes mellitus: from pathophysiology to clinical management. *Nat Rev Endocrinol*.2021; 17 (1): 11-30.
- [4] Papadogeorgakis N, Parara E, Petsinis V, Vourlakou C. A case of successfully treated rhinocerebral mucormycosis: Dental implications. *Intern J Density*.2010; 2010: 1-4.
- [5] Petrikos G, Skiada A, Lortholary O, Roilides E, Walsh TJ, Kontoyiannis DP. Epidemiology and clinical manifestations of mucormycosis. *Clin Infect Dis*.2012; 54 (suppl_1): S23-S34.
- [6] Mehta S, Pandey A. Rhino-orbital mucormycosis associated with COVID-19. *Cureus*.2020; 12 (9): e10726. doi: 10.7759/cureus.10726.
- [7] Song G, Liang G, Liu W. Fungal co-infections associated with global
- [8] OVID-19 pandemic: A clinical and diagnostic perspective from china. *Mycopathologia*.2020; 185: 599-606.
- [9] Meher R, Wadhwa V, Kumar V, et al. COVID associated mucormycosis: A preliminary study from a dedicated COVID hospital in delhi. *Am J Otolaryngol*.2022; 43 (1): 103220. doi: 10.1016/j.amjoto.2021.103220. Epub 2021 Sep 11.
- [10] Honavar S, Sen M, Lahane S, Lahane T, Parekh R. Mucor in a viral land: A tale of two pathogens. *Indian J Ophthalmol*.2021; 69 (2): 244-252.
- [11] Cornely OA, Alastruey-Izquierdo A, Arenz D, et al. Global guideline for the diagnosis and management of mucormycosis: An initiative of the european confederation of medical mycology in cooperation with the mycoses study group education and research consortium. *Lancet Infect Dis*.2019; 19 (12): e405-e421.