

Rhino Orbital Mucormycosis in Patients with RTPCR Positive COVID-19 Infection at A Tertiary Care Hospital

Kalpana Singh¹, Shewta Bandhopadhyay², Dhiraj Balwir³, Nikhil Charhate⁴, Nita Gngurde⁵, Jeetendra Singh⁶

¹Associate Professor, Department of Ophthalmology, Dr. Vasant Rao Pawar Medical College, Hospital and Research Centre, Adgaon, Nashik 422003, India

²Associate Professor, Department of Ophthalmology, Dr. Vasant Rao Pawar Medical College, Hospital and Research Centre, Adgaon, Nashik 422003, India

³Prof and Head, Department of Ophthalmology, Dr. Vasant Rao Pawar Medical College, Hospital and Research Centre, Adgaon, Nashik 422003, India

⁴Senior Resident-3rd year, Department of Ophthalmology, Dr. Vasant Rao Pawar Medical College, Hospital and Research Centre, Adgaon, Nashik 422003, India

⁵Prof and Head, Department of Microbiology, Dr. Vasant Rao Pawar Medical College, Hospital and Research Centre, Adgaon, Nashik 422003, India

⁶Prof and Head, Department of Pharmacology, Dr. Vasant Rao Pawar Medical College, Hospital and Research Centre, Adgaon, Nashik 422003, India

Received: 14-04-2023 / Revised: 18-05-2023 / Accepted: 11-06-2023

Corresponding author: Dr. Nita Gangurde

Conflict of interest: Nil

Abstract

Introduction: Corona virus disease (COVID-19) causes an immune-compromised state and increases susceptibility to various secondary infections like mucormycosis. Post-COVID-19 especially in the second wave there was a phenomenal increase in the cases of mucormycosis.

Aim: The aim of the study was to document the cases of rhino orbital mucormycosis presenting at our tertiary care institute during COVID-19 era and to study the outcome of these patients.

Materials and Methods: The study was a prospective hospital based study, conducted after the approval of Ethics committee. It was carried out from April 2021 to June 2021 in the tertiary care institute. All patients reported to us with diagnosed covid 19 infections along with clinical features, signs and symptoms of mucormycosis and microbiologically proven cases of mucormycosis were included. The diagnosis of covid 19 was based on RT-PCR test on nasopharyngeal / oropharyngeal swabs. The patients record included history taking, drug treatment, ophthalmological examination and radiological imaging studies. The patients were treated with intravenous amphotericin B, FESS (functional endoscopic sinus surgery). Retrobulbar injection of Amphotericin B or exenteration was decided case wise.

Results: Twenty patients were seen with the mean age of 49.95 years. The most common clinical symptom was ptosis in 85% cases, total external ophthalmoplegia in 65% cases and no perception of light (No PL) in 59.09% cases. Retrobulbar injection of Amphotericin B was given in 7 patients (35%) cases and exenteration was performed in 12 cases (60%) cases with a survival rate of 58.33%.

Conclusion: Retrobulbar injections of amphotericin B along with surgical debridement and systemic amphotericin B should be considered in patients of orbital mucormycosis who have definite orbital involvement but with minimal vision loss or are poor surgical candidates for exenteration.

Keywords: COVID-19, Mucormycosis, Exenteration, Retro Bulbar Injection.

This is an Open Access article that uses a funding model which does not charge readers or their institutions for access and distributed under the terms of the Creative Commons Attribution License (<http://creativecommons.org/licenses/by/4.0>) and the Budapest Open Access Initiative (<http://www.budapestopenaccessinitiative.org/read>), which permit unrestricted use, distribution, and reproduction in any medium, provided original work is properly credited.

Introduction

Corona virus disease 2019 (COVID-19) is a new viral disease caused by novel corona virus, Severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2). It was first detected in China in December 2019. The pathophysiology of COVID 19 is not completely understood but variety of new complications and manifestations of the disease are still being discovered. [1] Mucormycosis, also called as zygomycosis and phycomycosis, is a fungal infection. The fungus is ubiquitous in nature and is found in decaying food, air, soil other organic matter such as animal faeces. It is characterized by angioinvasion, vessel thrombosis, tissue necrosis. The most common clinical presentation of mucormycosis is rhino sinusitis followed by orbital infection and then cerebral involvement.[2] The most common fungal species causing sinus infection are *Aspergillus*, *Rhizopus*, *Rhizomucor* and *Mucor*. The spores inoculate the paranasal sinuses and the nasopharynx and spread aggressively to the surrounding orbits and intracranial cavity. Mucormycosis is classified depending upon the anatomic site of occurrence as 1) rhinocerebral, 2)orbital, 3) pulmonary, 4)cutaneous, 5) gastrointestinal and 6) disseminated. [3] Management of mucormycosis includes early diagnosis and rapid medical and surgical debridement. Lipid based Amphotericin B is effective in mucormycosis. [4] Some studies suggest early surgical debridement and orbital exenteration for mucormycosis. [5,6] but some authors have documented survival without exenteration (conservative approach). [7] There is still lack of well-defined guidelines for exenteration, and the decision to perform the procedure still rests with the treating physician. [8,9] Post COVID 19 especially in the second wave there was a phenomenal rise in the cases of

mucormycosis. We hereby present 20 cases of rhino orbital involvement of mucormycosis, in patients who had suffered with COVID-19.

Material and Methods: It was a prospective hospital based study. Study was done over a period of 3 months (between April 2021 to June 2021). Study was conducted at department of Ophthalmology of our centre. A total of 20 consecutive patients of mucormycosis with involvement of eye were enrolled (between 1st April 2021 to 30th June 2021).

Inclusion Criteria

1. All patients reporting to medical college and hospital with a proven case of covid 19 and clinical features, signs and symptoms of mucormycosis and microbiologically proven cases of mucormycosis. The diagnosis of covid 19 was based on RT-PCR test on nasopharyngeal/oropharyngeal swabs.
2. Orbital mucormycosis as a part of rhino-orbito cerebral mucormycosis.
3. Patients able and willing to give informed consent to participate in the study.

Exclusion Criteria

1. Unconscious and uncooperative patients, where correct visual acuity could not be recorded.
2. Patients with any ophthalmic symptoms of long duration (> 2 months)
3. Patient unwilling to give informed consent.

Patients presented with

- 1) Symptoms like headache, facial pain, proptosis, ptosis, diminution of vision, nasal symptoms like nasal discharge.
- 2) Radiological evidence of bone destruction and orbit/brain involvement

- 3) Tissue biopsy and pathological evidence of tissue invasion and vessel occlusion with presence of aseptate fungi in microbiological culture and
- 4) Concurrent or past history of COVID-19 infection. A complete history taking included history of any systemic diseases like Diabetes Mellitus or hypertension.

On day 1 of admission, blood sugar levels were checked. A complete ophthalmic examination included visual acuity, pupillary reaction, extraocular movements, slit lamp biomicroscopy and fundus examination. The diagnosis of COVID-19 was based on RT-PCR test. Patients were seen in the wards or in the eye out patient department (OPD) initially. Patients having positive clinical symptoms were advised magnetic resonance imaging (MRI) orbit, brain and computerized tomography (CT) paranasal sinuses for assessing the extent of the disease. Patients were managed along with ear, nose and throat (ENT), medicine and dental departments. Patients with proven mucormycosis were started on systemic amphotericin B (5 mg/kg/day upto 10 mg/kg/day for central nervous infections (CNS infections). Renal function

tests were repeated for any drug toxicity. Patients with uncontrolled diabetes were given insulin and/or oral antidiabetic drugs as per physician's advice. Patients were taken for Functional Endoscopic Sinus Surgery (FESS) and debridement and biopsy of the nasal tissue was sent for microbiological analysis and histopathology. Retrobulbar injection of Amphotericin B (3.5 mg/ml) or exenteration of eye was planned depending upon the severity of eye involvement. Exenteration was considered in patients with absent light perception and total ophthalmoplegia. Systemic amphotericin was continued for 14-21 days. Patients were discharged only after a negative nasal swab report. Tablet Posaconazole 300 mg once a day was continued orally after discharge for a minimum of 3 months as a protocol. The patients were followed up in ophthalmology OPD. A follow-up of at least 30 days was kept.

Results

A total of 20 patients presented to our centre between April 2021 and June 2021. The results are represented in a tabulated manner (tables 1 -4).

Table 1

Age (Years)	Number [Percentage (%)]
20-30	Nil
31-40	3(15)
41-50	8(40)
51-60	5(25)
61-70	4(20)
Gender	
Male	13(65)
Female	7(35)
Laterality	
Re Only	6(30)
Le Only	12(60)
Be	2(10)

The mean age of our patients was 49.95 years (range 30 years to 68 years).

Table 2

Risk Factors	Number (Percentage)
Dm	10(50)
Htn	3(15)
Ckd	1(5)
Chd	1(5)
Inj Remdesivir	5(25)
Intravenous Methylprednisolone	7(20)
Increased Bsl(R) In Undiagnosed Cases	10(50)
Oral Steroids	9(45)

All patients had high blood sugars on admission and half of the patients were undiagnosed cases of Diabetes. Steroid use was seen in 80% of patients. The duration between mucor symptoms and COVID-19 positivity was on an average 18.43 days.

Four cases were of newly diagnosed Diabetes Mellitus, when they presented with rhino orbital mucormycosis, six patients were of uncontrolled Diabetes Mellitus, rest were undiagnosed cases.

Table 3

Visual acuity	Total number [Percentage (%)]
6/6-6/18	2(10)
6/18p-6/60	Nil
<6/60-3/60	2(10)
<3/60-PL+	3(15)
NO PL	13(65)
Ophthalmological signs and symptoms	
Proptosis	3(15)
Ptosis	17(85)
Periorbital swelling	2(10)
Conjunctival chemosis	1(5)
Keratitis	1(5)
Necrosis	2 (10)
EOM Absent	13(65)
EOM restricted	5(25)
Eyelid swelling	2(10)
Facial pain	8(40)
Diminution of vision	5(25)
Headache	6(30)
Jaw ache	2(10)
Nasal block and bleed	4(20)
Pain in eye	2(10)
Facial swelling	3(15)
Facial palsy	1(5)
Significant Fundus Findings	
CRAO	3(15)
Vitritis	1(5)
Disc oedema	1(5)
Peripapillary Haemorrhage	1(5)
Pale Disc	1(5)

Table 4

Imaging Findings	Number of Cases (%)
Orbital Cellulitis	12(60)
Extraocular Muscle Involvement	4(20)
Optic Neuritis	1(5)
Bony Orbital Wall Invasion	12(60)
Pansinusitis	16(80)
Cavernous Sinus Thrombosis	2(10)
Cerebral Involvement	1(5)
Pons, Cerebellar Peduncles, Cerebellar Hemisphere	1(5)
Orbital Apex Involvement	3(15)
Merkels Cave and Skull Base Osteomyelitis	1(5)
Basifrontal Involvement	1(5)
Subdural Haemorrhage	1(5)
Treatment Of Mucormycosis	
Intravenous Amphotericin B	20 (100)
Sinus Debridement	20 (100)
Exenteration	12 (60)
Retrolbulbar Injection of Amphotericin B	7 (35)
Vitrectomy	1 (5)

The most common clinical symptom was ptosis in 85%, loss of extraocular movements (Total external ophthalmoplegia) and total loss of vision (No PL) in 65% cases. One patient presented with facial palsy and one patient had fungal endophthalmitis. On fundus examination three patients (15%) had Central retinal artery occlusion (CRAO) On radiological imaging, most common finding was pansinusitis in 16 patients (80%) followed by bony orbital wall erosion in 12 patients (60%). Cavernous sinus thrombosis was seen in 2 patients (10%). Intracranial involvement due to cerebral extension was seen in 2 cases (10%)

All patients received intravenous conventional or Liposomal Amphotericin B for 21 days (depending on the availability).

All patients underwent FESS procedure, retrolbulbar injection of Amphotericin B was given in 7 patients (35%) cases and exenteration was performed in 12 cases (60%) cases with a survival rate of 58.33%. Retrolbulbar injection of Amphotericin was given in patients who had orbital involvement on radiological imaging but had useful vision. Exenteration was performed in patients having No PL vision, total external ophthalmoplegia and radiological imaging findings of orbital involvement. Few salient features of case who were treated with reterobulbar injection and eyeball exenteration are shown as follows.

Case with Retrolbulbar amphotericin B injections:

[Image 1a (pre injection) and 1b (post 3 injections)]



(Produced with permission)

Case with Functional endoscopic sinus surgery, right eyeball exenteration and oral Posaconazole treatment:

[Image 1c (pre-operative) and 1d (post-operative after 2 months)]



(Produced with permission)

Discussion

Orbital mucormycosis is vision threatening and life threatening if not aggressively managed. It causes thrombosis, angioinvasion and tissue necrosis due to ischaemia. Mortality is between 50% to

80% with factors which include involvement of orbit and brain and irreversible immune suppression. [10,11] The patients become prone to infections due to compromised immune system with decreased CD4 + and CD8+ lymphocytes,

underlying systemic conditions such as Diabetes Mellitus and use of immunosuppressive drugs such as steroids in management of moderate to severe COVID cases. [12] Although all the complications of COVID infection are yet to be described and documented, secondary infections like invasive mucormycosis are being increasingly reported.

The genome of the prevalent SARS-CoV2 variant (B.1.1.7 & B.6.117) in India is believed to be the cause of the increased infection.[12,13] In the world, the incidence of mucormycosis is in the range from 0.0005 to 1.7 per million population, while in India the prevalence was 0.14 per 1000, approx 80 times more than the developed countries.[14,15] In the normal individuals, the spores and hyphae are taken up and destroyed by mononuclear and polymorphonuclear phagocytes. When patients have a low phagocyte count, impaired phagocyte function, neutropenia or poorly controlled Diabetes mellitus, they become susceptible to fungal infection[16]. In mucormycosis the site of entry is nose and paranasal sinuses are first involved. If proper treatment is not started early, the spread of infection to adjacent structures may occur. The orbit can be involved via lamina papyracea of ethmoid bone, inferior orbital fissure, infratemporal fossa or orbital apex. Involvement of brain occurs through ethmoid cribriform plate, supraorbital fissure. Other intracranial complications include cavernous sinus thrombosis, cerebral infarction, intracranial haemorrhage and cerebral abscess. [17]

In our study, the mean age of presentation was 49.95 years with a skew deviation towards male gender (65%), females involvement being 35%. The most common risk factor was Diabetes Mellitus (100%). Use of steroids during management of moderate to severe cases of COVID further reduced the immunity in 80% patients. The use of steroid led to impaired blood glucose levels or uncontrolled Diabetes leading to rise in mucormycosis cases. Similar finding

was seen in studies of Ravani et al and Mrittika Sen et al[18,19].

Mucormycosis is not easy to diagnose, a delay of even six days in initiating treatment doubles the 30 day mortality from 35% to 66%. [1] Orbital apex syndrome was the most common presenting symptom in our study. Similar finding was seen in study by Allister S Lee et al. [4]

In our study, 7 patients were treated with retrobulbar injections of amphotericin B. Retrobulbar injections were given in patients where there was orbital involvement but useful vision was present in the eye. Retrobulbar injection consisted of AMB deoxycholate (1 ml of 3.5 mg/ml) with antecedent retrobulbar injection of anaesthetic (1 ml of 2% lidocaine), a good digital massage was given post injection to prevent compartment syndrome. The number of injections ranged from 1 to 4 injections. Response was checked with measurement of visual acuity. The benefit of local administering AMB is due to the angioinvasive nature of the disease which limits tissue penetration of systemic antifungals. Retrobulbar injection of AMB is an off label application and has associated risks. Multiple reports have shown that retrobulbar injections are successful in treatment of orbital mucormycosis without visual loss but there is associated risk of neurotoxicity and cytotoxicity. [20-23] Only in one patient transient inflammation and soft tissue edema was seen post retrobulbar injection of amphotericin B.

Orbital exenteration was done in cases with no perception of light, extraocular movements absent and fixed, dilated pupil. The aim of the operation was to debulk the ischaemic and necrotic tissue which helps in fungus to grow and preventing the spread of infection to the cavernous sinus and cerebrum. The clear guidelines for exenteration of orbit in cases of mucormycosis are still not defined, and the decision still lies primarily with the treating physicians.[8] Twelve mucormycosis

patients underwent exenteration with seven surviving (58.33%).

Conclusion

Retrobulbar injections of amphotericin B along with surgical debridement and systemic amphotericin B should be considered in patients of orbital mucormycosis who have definite orbital involvement but with minimal vision loss or are poor surgical candidates for exenteration. Corticosteroids which are used in the management of moderate to severe mucormycosis should be used judiciously and its unwanted and irrational use should be prevented as most of the cases of mucormycosis were either having pre-existing Diabetes or were given steroids during COVID treatment and now had high blood sugar levels. Management of mucormycosis patients is a team effort, from Covid care doctors, ophthalmologists, the medicine colleagues, ENT specialists, neurosurgeons, dieticians, microbiologists and pathologists all have to be actively involved in management of mucormycosis. Mucormycosis is a very aggressively growing disease and requires prompt diagnosis and treatment. Delayed diagnosis increases mortality

Conclusive Remarks: Retrobulbar injections of amphotericin B should be considered in patients of orbital mucormycosis who have definite orbital involvement but with minimal vision loss or are poor surgical candidates for exenteration.

References

1. Amanda Werthman-Ehrenreich.; Mucormycosis with orbital compartment syndrome in a patient with COVID-19. *Am J Emerg Med.* 2021 Apr; 42:264. e5-264.e8
2. Neha Mishra, Venkata Sai Shashank Mutya, Alphonsa Thomas, Girish Rai, Bathi Reddy, Anithakumari Alnipully Mohanan et al.; A case series of invasive mucormycosis in patients with COVID-19 infection. *International*

- Journal of Otorhinolaryngology and Head and Neck Surgery. May 2021;7(5): 867-70.
3. Papadogeorgakis N, Parara E, Petsinis V, Vourlakou C.; A case of successfully treated rhinocerebral mucormycosis: dental implications. *Int J Dent.* 2010; 2010:273127.
4. Allister S. Lee, Princeton W. Y. Lee, Anthony Allworth, Tai Smith, Timothy J.; Sullivan. Orbital mycoses in an adult subtropical population, *Eye.* 2020; 34:1640-47
5. R A Yohai, J D Bullock, A A Aziz, R J Markert.; Survival factors in rhino-orbital-cerebral mucormycosis. *Surv Ophthalmol.* Jul-Aug 1994;39(1):3-22.
6. R W Pelton, E A Peterson, B C Patel, K Davis.; Successful treatment of rhino-orbital mucormycosis without exenteration: the use of multiple treatment modalities, *Ophthalmic Plast Reconstr Surg.* 2001 Jan;17(1):62-6.
7. Athavale DD, Jones R, O'Donnell BA, Forer M, Biggs N; Non-exenteration management of sino-orbital fungal disease.; *Ophthalmic Plast Reconstr Surg.* Nov-Dec 2017;33(6):426-9.
8. Hargrove RN, Wesley RE, Klippenstein KA, Fleming JC, Haik BG.; Indications for orbital exenteration in mucormycosis. *Ophthal Plast Reconstr Surg.* July-Aug 2006;22(4):286-91.
9. Oliver A Cornely, Ana Alastruey-Izquierdo, Dorothee Arenz, Sharon C A Chen, Eric Dannaoui, Bruno Hochhegger 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 9 December; 19(12): e405-e421.
10. Zesemayat K Mekonnen, Davin C Ashraf, Tyler Jankowski, Seanna R Grob, M Reza Vagefi, Robert C Kersten et al.; Acute Invasive Rhino-Orbital Mucormycosis in a Patient With COVID-19 Associated Acute

- Respiratory Distress Syndrome. *Ophthalmic Plast Reconstr Surg.* 2021 Mar-Apr 01;37(2):e40-e80.
11. Berenice Morales-Franco, Mario Nava-Villalba, Edgar Octavio Medina-Guerrero, Yair Adonai Sánchez-Nuño, Perla Davila-Villa, Elsa Janneth Anaya-Ambriz et al.; Host-pathogen molecular factors contribute to the pathogenesis of *Rhizopus* spp. in diabetes mellitus. *Current Trop Med Reports.* 2021; 8: 6-17.
 12. Vaidyanathan G.; Coronavirus variants are spreading in India — what scientists know so far. *Nature.* 2021; May; 593(7859):321-22.
 13. Mehta S, Pandey A.; Rhino-orbital mucormycosis associated with COVID-19. *Cureus* 12(9): e10726
 14. Jagdish Chander, Mandeep Kaur, Nidhi Singla, R P S Punia, Surinder K Singhal, Ashok K Attri et al.; Mucormycosis: battle with the deadly enemy over a five-year period in India. *J Fungi (Basel).* 2018; Apr 6; 4(2)
 15. Prakash H, Chakrabarti A.; Global epidemiology of mucormycosis. *J Fungi (Basel).* 2019; Mar 21; 5(1):26
 16. Kirill Alekseyev, Lidiya Didenko, and Bilal Chaudhry.; Rhinocerebral Mucormycosis and COVID-19 Pneumonia, *J Med Cases.* 2021 Mar; 12(3): 85–89
 17. Lav Selarka, Suktara Sharma, Dinesh Saini, Sanjay Sharma, Amit Batra, Vishal T. Waghmare et Al.; Mucormycosis and COVID-19: An epidemic within a pandemic in India. wileyonlinelibrary.com, <https://doi.org/10.1111/myc.13353>. Assessed on 11 November 2022
 18. Mrityika Sen, Sumeet Lahane, Tatyrao P Lahane, Ragini Parekh, Santosh G Honavar.; Mucor in a Viral Land: A Tale of Two Pathogens, *Indian J Ophthalmol.* 2021, Feb;69(2):244-52.
 19. Swati A Ravani, Garima A Agrawal, Parth A Leuva, Palak H Modi, Krisha D Amin.; Rise of the phoenix, Mucormycosis in COVID-19 times, *Indian Journal of Ophthalmology:* June 2021; 69(6): 1563-68.
 20. Seiff S.R., Choo P.H., Carter S.R.; Role of local amphotericin B therapy for sino-orbital fungal infections. *Ophthalmic Plast Reconstr Surg.* 1999; 15(1): 28-31
 21. Joos Z.P., Patel B.C.; Intraorbital irrigation of amphotericin B in the treatment of rhino-orbital mucormycosis. *Ophthalmic Plast Reconstr Surg.* 2017;33(1), 13-16
 22. Frank L. Brodie, Evan Kalin-Hajdu, Debbie S. Kuo, Kristin E. Hirabayashi, Reza Vagefi, Robert C. Kersten.; Orbital compartment syndrome following retrobulbar injection of amphotericin B for invasive fungal disease. *Am J Ophthalmol Case Rep.* 2016 Apr; 1: 8–10.
 23. Kristin E Hirabayashi, Evan Kalin-Hajdu, Frank L Brodie, Robert C Kersten, Matthew S Russell, M Reza Vagefi.; Retrobulbar Injection of Amphotericin B for Orbital Mucormycosis. *Ophthalmic Plast Reconstr Surg.* Jul/Aug 2017;33(4): 94-97.