



## OCULAR PRESENTATION IN POST COVID MUCORMYCOSIS PATIENTS

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**ABSTRACT** **Aims & Objective:** 1. To study the association between COVID 19 & known risk factors of opportunistic fungal infection of mucormycosis.

2. To study the safety and efficacy of retrobulbar inj. amphotericin B

**Methods:** This is Cross-Sectional study conducted in tertiary care centre over 2 months on 151 consecutive patients diagnosed with COVID 19 & developed Rhino-orbital cerebral mucormycosis, diagnosis is made from clinical presentations, CT/MRI, KOH staining & culture of nasal swab & endonasal biopsy.

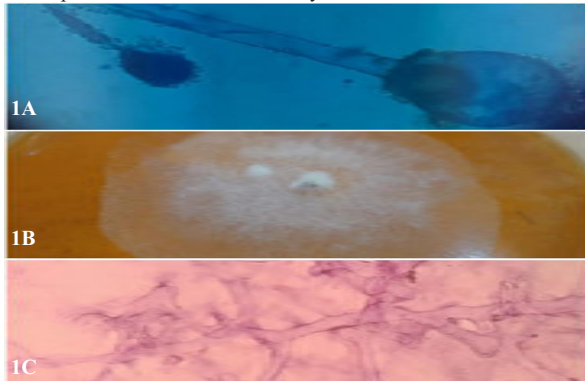
**Results:** All patients presenting with rhino-orbital cerebral mucormycosis, had an association with coronavirus disease 2019. orbital involvement was seen in 53.64 % cases, Uncontrolled diabetes mellitus was present in 88.88% cases, 75.30% patients had history of steroid use during their coronavirus treatment. 72.83 % male & 27.16 % female were affected. 72.83% patients had required oxygen therapy at the time of COVID19 infection. 77.77% patients had been infected with COVID-19 previously while 22.22% tested covid + at the time of presentation of rhino-orbital cerebral Mucormycosis. 76.54 % of patients were treated with retrobulbar & systemic inj. of amphotericin b with +/- sinus debridement, while 3 pts required exenteration along with systemic amphotericin b & sinus debridement.

**Conclusion:** The association between COVID 19 and rhino-orbital cerebral mucormycosis requires serious consideration. Moderate to severe cases of COVID19 , extensive use of steroids, long term oxygen therapy & uncontrolled diabetes are associated with common opportunistic fungal infection of mucormycosis. Rhino-orbital cerebral mucormycosis is best managed by a multidisciplinary team. All cases of rhino orbital cerebral mucormycosis requires immediate initiation of i.v.amphotericin b. Mild to Moderate cases can be treated with two doses of Transcaruncle inj of retrobulbar amphotericin b which may allow for orbit & globe preservation. Severe cases required Exenteration. Early diagnosis & aggressive treatment can not only save life but also the globe!

**KEYWORDS :** Rhino-orbital-cerebral mucormycosis, COVID-19, Retrobulbar inj. amphotericin b (RBB)

## INTRODUCTION

As the global COVID-19 pandemic spreads worldwide, new challenges arise in the clinical landscape, the growing risks of co-infections, is a major threat not only to the health system but also to patient's life. Over the past few months, sudden rise in cases of invasive fungal sinusitis, specifically mucormycosis in post covid & covid patients is seen in our institute. Mucormycosis is rapidly progressing fungal infection which is caused by non-septate filamentous fungi in the Mucoraceae family and it is frequently seen in diabetic and immunocompromised patients. The 2019 novel coronavirus (2019-nCoV) or severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) first reported in Wuhan, Hubei province in China, quickly spread to other parts of the world forming a global pandemic<sup>[1]</sup> There are reports of the development of severe opportunistic infections such as oropharyngeal candidiasis, pneumocystis jiroveci pneumonia, pulmonary aspergillosis, bloodstream candida infections, etc., in patients affected with COVID-19 disease.<sup>[2]</sup> There are also few isolated case reports of rhino-orbital mucormycosis in COVID-19 disease.<sup>[3,4]</sup>



**Fig 1.** Microbiological image of Mucormycosis.

Rhino-orbital infection develops when spores of the fungi are inhaled and invade the nasal mucosa, and sinusitis develops as the fungus spreads to the paranasal sinuses. Orbital involvement occurs when the infection invades medial orbital wall/floor of orbit from the paranasal sinuses. Symptoms include periorbital pain, chemosis, vision loss, ophthalmoplegia and proptosis. Ophthalmoplegia arises from infection of the muscles and orbital space or when the third, fourth and sixth cranial nerves are affected. Seventh cranial nerve paresis or paralysis and hypoesthesia of the face is often observed<sup>[5,6]</sup>

Clinically, rhino-orbital cerebral mucormycosis can present with atypical signs and symptoms similar to complicated sinusitis, such as nasal blockade, crusting, proptosis, facial pain and oedema, ptosis, chemosis, and even ophthalmoplegia, with headache and fever and various neurological signs and symptoms if intracranial extension is present.<sup>[7,8]</sup> Without early diagnosis and treatment, there may be rapid progression of the disease, with reported mortality rates from intra-orbital and intracranial complications of 50–80 per cent<sup>[9]</sup> Even with prompt diagnosis, treatment of underlying diseases, and aggressive medical and surgical intervention, the management is often not effective, leading to an extension of the infection and ultimately death.<sup>[10]</sup> A complex interplay of factors that include diabetes mellitus, any previous respiratory pathology, immunosuppressive therapy, nosocomial infection sources and systemic immune alterations of Covid-19 recognised in view of their impact on morbidity and mortality.<sup>[11]</sup>

In this 2<sup>nd</sup> wave of pandemic which started in February 2021 , we have experienced sudden rise in number of Rhino-orbital cerebral mucormycosis cases associated with COVID19. Here we are sharing our experience of managing these cases.

## MATERIALS AND METHODS

This is a Cross-Sectional study, conducted in tertiary care center on 151 consecutive patients over 2 months, from April to May 2021 after

taking the approval of ethical committee. All patients with invasive mucormycosis, who were either coronavirus-positive or had recovered from corona virus illness, were included in the study. Details of all patient's including clinical features, CT/MRI findings, associated co-morbidities & management were recorded & analyzed. All patients of Rhino-orbital cerebral mucormycosis were categorized in to mild, moderate & severe cases on the basis of their clinical presentation and imaging. The treatment protocol followed here was as follows (Table 1).

**Table 1: Treatment Protocol**

Mild to moderate cases	I.V amphotericin B + Retrobulbar Injection of Amphotericin B +/- FESS
Severe cases	I.V amphotericin B + Exenteration +/- FESS

**RESULTS:**

A total of 151 patients presented as Rhino-orbital cerebral mucormycosis; of these 81 patients had ocular involvement. 59 patients were male and 22 patients were female. Of this 63 had been infected with COVID earlier and had recovered and 18 of the patients were newly diagnosed for COVID along with mucormycosis (Table 2). In this study incidence of Rino-orbital cerebral mucormycosis was (77.77%) in post covid patients.

**Table 2: Incidence Of COVID & Post- COVID Patients**

	No. of covid Treated positive patients	Newly diagnosed covid19 positive patients along with mucormycosis	Total
Male	48	11	59
Female	15	7	22
Total	63	18	

Of these previously treated COVID19 patients, no. of patients treated with steroids/other immunosuppressant's (Table 3) is tabulated as below:

**Table 3: Incidence Of Patients On Steroids**

	Patients on steroids / immunosuppressant	Never on steroids	Total
Male	45	14	59
Female	16	6	22
Total	61	20	

In our study, it is commonly seen in patients who had been infected with COVID earlier & were on steroids for longer duration (75.30%).

Association between use of O2 therapy for treatment of COVID19 and development of Mucormycosis was also seen (Table 4)

**Table 4: Incidence Of Patient's On O2**

	No. of Patients on O2 support at the time of Covid19 infection	No. of patients not requiring O2 support at the time of COVID19 infection	Total
Male	45	14	59
Female	14	8	22
Total	59	22	

It was found that patient who have developed severe COVID19 infection requiring O2 therapy were more prone to develop mucormycosis than those have mild COVID19 illness (72.83%).

72 (88.88%) patients were diabetic & 9 (11.11%) were non diabetic (Table 5); all had uncontrolled blood sugar levels with haemoglobin A1c levels higher than 6 per cent, and 14 patients had hypertension; all of these were diabetic. One patient was in renal failure at the time of presentation.

**Table 5: Incidence Of Diabetic & Non Diabetic Patients**

	Status	Cases (in %)
Diabetes mellitus	uncontrolled	72
Non diabetes	uncontrolled	9

Of the 151 patients, 81 had ocular involvement at the time of presentation. 27 had severe vision loss, 35 had mild to mod visual loss and 19 had no complaints of vision loss at presentation. The classical Black eschar on eyelid was observed in 4 patients. Depending on

ocular symptoms at presentation, patients were classified as having mild, moderate and severe disease as follows (Table 6):

Mild symptoms : Clinical features + ( mild lid oedema , mild ptosis )  
With/ without ocular involvement on CT scan.

Moderate symptoms : Clinical features + ( Orbital Apex Syndrome, lid edema , Proptosis, mild-moderate extraocular movement Restriction , chemosis, ptosis).  
With ocular involvement on CT scan

Severe symptoms : Optic nerve involvement, intracranial extension  
with Extensive involvement on CT scan.

**Table 6: Incidence Of Mild, Moderate And Severe Mucormycosis Cases**

Symptoms	Mild	Moderate	Severe	Total
Male	15	33	11	57
Female	10	8	4	22
Total	25	41	15	

Most of the patient presented in our hospital had mild-moderate involvement (81.47%). Only 18.51% of the total patients had presented with extensive involvement.

Of these patients, 62 (76.54%) received 2 injections of transcaruncle retrobulbar amphotericin b (3.5mg/ml). RBB was administered after 1-2cc of local lignocaine block. these two inj of RBB are given 3days apart. 3 patients required orbital exenteration. 11 patients had very minimal disease and were treated on I.V amphotericin b along with sinus surgery. 5 patients were critically ill and were considered unfit for Retrobulbar injection/surgery by anesthetist, hence were treated only on I.V amphotericin b (Table 7).

**Table 7: Various Modalities Of Treatment Used**

	No. of patients who were treated on I.V amphotericin b +/- FESS	No. of patients treated with RBB +I.V amphotericin B +/-FESS surgery	No. of patients treated with exenteration + I.V amphotericin B + FESS surgery	Total
Male	12	44	3	59
Female	4	18	0	22
Total	16	62	3	

35 had mild to mod visual loss and 19 had no complaints of vision loss at presentation. Vision of these 54 patients did not deteriorate throughout the course of treatment in our hospital. Out of the 81 patients, 11 deaths were reported secondary to COVID 19 complications.



**Fig(2)** Picture showing Orbital Apex Syndrome, as seen in most patients in our hospital





**Fig 3:** (3a): Above is the image of a patient who had presented with ptosis, conjunctival congestion & chemosis, restricted extraocular movements, (3d) with CT image showing destruction of left lamina papyracea suggestive of Orbital Mucormycosis. The patient was started on i.v amphotericin b & retrobulbar injection of Amphotericin B. (3b) shows improvement after 1<sup>st</sup> dose of Retrobulbar Amphotericin B. (3 c) shows improvement after 2<sup>nd</sup> dose of I.V amphotericin b.



**Fig 4,** (4a):on presentation : ptosis+ ,mild proptosis with restricted eom ,(4d) CT s/o erosion of lamina papyracea with fat stranding in extraconal compartment. Image (4b) & (4c) shows improvement post 1<sup>st</sup> and 2<sup>nd</sup> dose of retrobulbar injection respectively.



**Fig 5,** Above is the image (5a)(5b) of the patient who had presented with lid oedema with severe ptosis , with no Vision (pl-) with restricted extraocular movements with extensive involvement on CT scan, (5c) Pt had to be exenterated due to extensive involvement.

#### DISCUSSION:

Known risk factors associated with development of Rhino-orbital cerebral Mucormycosis as suggested by few studies<sup>[2,3,12,13,14]</sup> in COVID19 patients are as follows:

1. Diabetes Mellitus
2. Use of higher I.V antibiotics
3. Steroids/other immunosuppressant
4. O2 therapy

Out of the total 151 Rhino-orbital cerebral Mucormycosis cases reported in our hospital in the month of April-May 2021, 53.64% patients had Orbital involvement and were included in this study. Out of 81 patients, 72.83% were male, suggesting a male preponderance. All of the 81 patients were tested COVID19 positive either previously or were positive at the time of presentation. Not a single case of Rhino orbital cerebral mucormycosis was reported in a COVID19 negative patient.

Out of the total 81 patients, 75.30% patients who developed mucormycosis were treated with steroids/immunosuppressant and 72.83% patients required Oxygen support during the treatment of COVID19 infection.

In our study 88.88% patients were known diabetics, but all 81 patients had uncontrolled blood sugar levels at the time of presentation.

43.20% had mild to moderate vision loss at the time of presentation and 23.45% patients had no visual complaints at the time of

presentation. All patients either maintained their visual acuity or showed improvement post retrobulbar injection Amphotericin B.

Amphotericin-B deoxycholate remains the anti-fungal treatment of choice to start, with its liposomal preparations preferred because of decreased nephrotoxicity. In this study all Patients had received Amphotericin-B deoxycholate. Challenges in treating ROCM is due in part to its underlying pathogenesis in which endothelial cell damage leads to vascular thrombosis decreasing the efficacy of systemic antifungals.<sup>[15]</sup>

Retrobulbar amphotericin B injection is an infrequently reported globe-sparing technique that can aid in the management of invasive sino-orbital aspergillosis. To our knowledge, of the previously published cases of sino-orbital aspergillosis have employed retrobulbar injections of amphotericin B. In these reports, the quantity of amphotericin B administered ranged from 1 to 5.25 mg every 2–7 days. In all cases, retrobulbar injections were without complication and VA was maintained or improved. However, in two cases patients eventually succumbed to systemic infection<sup>[16]</sup>.

Transcutaneous retrobulbar inj. Of amphotericin B is the alternative means of treatment to achieve higher doses of the drug at the site of infection. In this study mild to moderate cases i.e 76.54% of patients had been treated with 2 injections of Transcaruncle retrobulbar amphotericin B (3.5mg), 3 days apart along with systemic amphotericin B with or without FESS by ENT specialist. Vision is saved in 27.16% , globe is preserved in 71.60% of cases after retrobulbar injection of amphotericin b . Retrobulbar injection of amphotericin B is a globe sparing technique in mild to moderate cases of rhino-orbital cerebral mucormycosis. In all of our cases , no major complications were reported post retrobulbar injection and Visual acuity was either maintained or improved. However in few patients transient orbital inflammation is observed but it got resolved within 4-5 days after 2<sup>nd</sup> dose of retrobulbar amphotericin b . This intervention is a viable therapeutic option in mild to moderate cases of orbital mucormycosis where the burden of orbital disease is not substantial. Better cosmetic and psychological results can be achieved with this technique.this effective role of intraconal amphotericin b was also mentioned by Luna JD et al<sup>[17]</sup>. 3 patients who had severe involvement with no visual potential had been treated with Exenteration.

#### SUMMARY :

In our study ,

- Out of the total 151 patients of ROCM , 53.64% patients had orbital involvement
- Males (72.83%) were more commonly affected than females (27.16%)
- All patients were either COVID19 Positive at the time of presentation or were tested positive previously
- 75.30% patients were on steroids.
- 72.83% patients required O2 therapy at the time of COVID19 infection.
- 88.88% were known diabetics , but all patients had uncontrolled blood sugar level.
- 81.47% people had mild- moderate ocular involvement at the time of presentation and 18.51% people had severe involvement.
- Retrobulbar injection Amphotericin B was administered in 76.54% of the total patients
- Vision is saved in 27.16% , globe is preserved in 71.60% of cases after retrobulbar injection of amphotericin b.
- All patients either maintained their visual acuity or showed improvement post retrobulbar injection of Amphotericin B

#### CONCLUSION

The association between COVID 19 and rhino-orbital cerebral mucormycosis requires serious consideration. Moderate to severe cases of COVID19 , extensive use of steroids, long term oxygen therapy & uncontrolled diabetes are associated with common opportunistic fungal infection of mucormycosis. Rhino-orbital cerebral mucormycosis is best managed by a multidisciplinary team. All cases of rhino orbital cerebral mucormycosis requires immediate initiation of i.v.amphotericin b. Mild to Moderate cases can be treated with Transcaruncle inj of retrobulbar amphotericin b which may allow for orbit & globe preservation. Severe cases required Exenteration. Early diagnosis & aggressive treatment can not only save life but also the globe.Standard treatment for Mucormycosis is I.V amphotericin B +/- FESS +/- Exenteration, however Retrobulbar



amphotericin B is a safe and effective option in mild to moderate cases of mucormycosis in order to preserve the globe and limit the spread of disease.

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