

Clinical Study and Outcome of Rhino-Orbital Mucormycosis Patients

Swati Sonwalkar*

Department of Ophthalmology, Jadavpur University, Kolkata, India

ABSTRACT

Objectives: To know the clinical presentation and outcome of rhino-orbital-cerebral mucormycosis during the limited availability of facilities during the acute surge of COVID 19 pandemic.

Method: we conducted a retrospective, non-interventional observational study on 55 patients with rhino-orbital-cerebral mucormycosis. The study was undertaken based on the data available from case records that were diagnosed with Rhino-Orbital mucormycosis.

Results: The mean age was 51.1 ± 11.3 years with a male preponderance of 72.7%. 50% of patients were receiving treatment in mucormycosis ward. Concurrent on going COVID-19 with ROCM and past history of COVID-19 was present in 49.1% and 34.5% respectively. History of steroid usage was seen in 81.81% of cases. Old case of diabetes and newly diagnosed diabetics were 47.3% and 32.7% respectively. The most common clinical presentation was proptosis (65.5%), partial ophthalmoplegia (65.6%) and ptosis (50.9%), with highest number of patients involving orbital apex (34%). Injection amphotericin B, TRAMB, FESS, FESS with orbital debridement and exenteration was done in 76.4%, 74.5%, 72.7%, 32.4% and 1.8% respectively.

Conclusion: Mucormycosis should be suspected in patients with COVID-19 irrespective of severity with history of steroid usage associated with diabetes mellitus in second and third week. Our study signifies the importance of early diagnosis and prompt initiation of treatment with systemic, transcutaneous retrobulbar amphotericin B injection and debridement of the orbit helps to salvage eye without requiring orbital exenteration. Even during scarcity of drugs and inadequately equipped health system we were still able to salvage eyes in maximum number of patients.

Keywords: Rhino-orbital-cerebral mucormycosis; COVID-19; Transcutaneous retrobulbar amphotericin B

INTRODUCTION

Mucormycosis is an aggressive and angioinvasive fungal infection with high risk of mortality also known as phycomycosis and zygomyces. It is caused by the organism from Mucoraceae family with *Mucor*, *Rhizopus* and *Absidia* species [1].

Fungus invades the paranasal sinus mucosa and cause sinusitis, and then may spread to orbit or directly to orbital apex and from there gain access intracerebral. It typically has rapidly progressing presentation and disease is associated with a high mortality rate [2].

Mucormycosis is usually reported in those COVID 19 patients who had weak immune system or immunocompromised

including those with hematological malignancy, diabetes mellitus, patients on steroids, neutropenia, chronic kidney diseases stem cell transplantation [3-5].

The probable reasons for high mortality include a delay in diagnosis, high cost of managing mucormycosis. Further worsening of crisis of mucormycosis by an acute scarcity of amphotericin B caused by large number of cases of mucormycosis. Due to limited availability or non-availability of amphotericin B, posaconazole or isavuconazole lead to imperative use of alternative antifungals with adequately equipped health system with all necessary drugs would help to tackle the situation in future.

Correspondence to: Swati Sonwalkar, Department of Ophthalmology, Jadavpur University, Kolkata, India, Tel: 7411481224; E-mail: sonwalkarswati97@gmail.com

Received: 20-Jul-2022, Manuscript No. JCEO-22-18505; **Editor assigned:** 23-Jul-2022, PreQC No. JCEO-22-18505 (PQ); **Reviewed:** 06-Aug-2022, QC No. JCEO-22-18505; **Revised:** 31-Oct-2022, Manuscript No. JCEO-22-18505 (R); **Published:** 30-Mar-2023, DOI: 10.35248/2155-9554.23.14.943

Citation: Sonwalkar S (2023) Clinical Study and Outcome of Rhino-Orbital Mucormycosis Patients. J Clin Exp Ophthalmol. 14:943.

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MATERIALS AND METHODS

The study was undertaken depending on the data available of the patients from case records who were diagnosed with rhino-orbital mucormycosis.

- Case records of those patients satisfying the inclusion and exclusion criteria were collected.
- Demographic data with detailed history, including ocular complaints and complete history of concomitant systemic illness with their treatment available in records were noted.
- Patients with possible Rhino-Orbital-Cerebral Mucormycosis (ROCM) that is typical symptoms and signs in the clinical setting of concurrent or recently (<6 weeks) treated COVID

19, diabetes mellitus, immunosuppression, use of systemic steroids and tocilizumab, mechanical ventilation or supplemental oxygen and probable ROCM patients that is supportive evidence clinically and on diagnostic nasal endoscopy and/or contrast enhanced MRI/CT scan and proven ROCM that is with confirmation on direct microscopy or culture or histopathology with special stains or molecular diagnostics.

- The severity of the COVID-19 disease will be graded based on High resolution computed tomography thorax data available (Table 1).

Table 1: HR-CT grading.

score	HR-CT grading
<8%	Mild
9%-15%	Moderate
>15%	Severe

The details of visual acuity and ocular examination done under torch light and fundus examination done bedside using indirect ophthalmoscopy. The details of medical treatment which includes injection amphotericin B, tablet posaconazole, surgical interventions done by ENT and ophthalmology department which includes retrobulbar amphotericin B injection and Functional Endoscopic Sinus Surgery (FESS), extended orbital debridement and orbital exenteration based on the condition of the patient will be included.

fourth (32.7%), fifth decade (29.1%) of life. Mean age was 51.1 ± 11.3 years with male preponderance (72.7%). Among the total number of cases 50% of patients received treatment in mucormycosis, 34.5% in COVID ward, 9.1% in ICU and 5.5% in SARI ward (Tables 2 and 3).

RESULTS

Data of 55 patients of ROCM with associated COVID 19 was retrieved from the case records. Most of the patients were in

Table 2: Demographic data.

Age groups	No of cases	Percentage
21-30	1	1.8
31-40	10	18.2
41-50	18	32.7
51-60	16	29.1
61-70	9	16.4
71-80	1	1.8
Sex		
Male	40	72.7
Female	15	27.3
Eye		

BE	2	3.6
LE	28	50.9
RE	25	45.5

BE=Both Eyes, LE=left Eye, RE=right Eye.

Table 3: Place of receiving treatment.

WARD	No. of cases	Percentage (%)
CW	19	34.5
ICU	5	9.1
MW	28	50.9
SARI	3	5.5
Total	55	100

CW=COVID Ward; ICU=Intensive Care Unit; MW=Mucor Ward; SARI=Sever Acute Respiratory Infection.

Systemic association

Out of 55 patients, concurrent on going COVID-19 with ROCM was seen in 27 patients at the time of diagnosis, past history of COVID-19 was present in 19 patients and 9 patients had no positive history of COVID-19. COVID-19 grading was done based on HR CT thorax. Mild, moderate and severe COVID-19 grade was present in 9, 24 and 13 patients respectively. 26 patients were known case of diabetes mellitus

and 18 cases were newly diagnosed diabetic, 5 patients were hypertensive, chronic kidney disease was present in 1 patient and 11 patients had no comorbidities. History of steroid usage (Dexamethasone and methylprednisolone) during the course of COVID-19 treatment was present in 45 patients and mean duration of steroid usage was 8.39 ± 2.5 days (Table 4).

Table 4: Covid status and co morbidity.

		No. of cases	%
COVID: Positive	Positive	27	49.1
COVID-History	Present	19	34.5
	Absent	9	16.4
Co morbidity	DM	26	47.3
	NDM	18	32.7
	HTN	5	9.1
	CKD	1	1.8
	NONE	11	20
Steroid usage	Present (D/MP)	45	81.81
	Absent	10	18.18

DM=Diabetes Mellitu; NDM=Newly Detected Diabetes Mellitus; HTN=Hypertension; CKD=Chronic Kidney Disease; D=Dexamethasone; MP=Methylprednisolone

Symptoms and signs and the site of involvement of ROCM

The most common clinical presentation was proptosis (65.5%), partial ophthalmoplegia (65.6%) and ptosis in 50.9%. Loss of vision with no perception of light was seen in 18.2% of cases. Other presentations were, total ophthalmoplegia (34.5%), retinitis (1.8%), CRAO (5.4%) and CRVO (1.8%). The most common site of involvement based on clinical and radiological

imaging was orbital apex (34.55%). Other findings on radiological imaging was peri-orbital cellulitis (25.45%), orbital cellulitis (12.7%), myositis, retro orbital neuritis, superior orbital fissure was involved in 10.9%, cavernous sinus (7.27%), pulmonary involvement with rhino-orbital involvement was seen in 1.8% (Table 5).

Table 5: Ocular signs and symptoms of mucormycosis at presentation.

Visual acuity	No. of cases	%
CF>5 mt	32	58.18
CF<5 mt to PL ^{+ve}	13	23.6
PL ^{ve}	10	18.2
Proptosis	36	65.4
Ptosis	28	50.9
Retinitis	1	1.8
CRAO	3	5.4
CRVO	1	1.8
Partial ophthalmoplegia	36	65.5
Total ophthalmoplegia	19	34.5

CF: Counting Finger; PL^{ve}: Loss of Light Perception; EOM: Extra Ocular Movements; CRAO: Central Retinal Artery Occlusion; L: Limited; A: Absent; CRVO: Central Retinal Vein Occlusion.

Table 6: Site of involvement based on clinical and radiological finding.

Diagnosis	No. of cases	%
POC	14	25.45
OC	7	12.7
SOF	6	10.9
OA	19	34.55
CVS	4	7.27
Myositis	3	5.5
OC+Pulmonary	1	1.8
RBN	1	1.8
Total	55	100

POC=Peri-Orbital Cellulitis; OC=Orbital Cellulitis; SOF=Superior Orbital Fissure; OA=Orbital Apex; CVS=Cavernous Sinus; RBN=Retrobulbar Neuritis

Staging of ROCM

- The staging was done based on proposed staging system of ROCM 8.
- Maximum number of patients were in stage 3c (50%) and in stage 3b (32.7%). 7.3% were in stage 3a, 5.5% in 4a, 1.8% each in 4b and 3d (Table 7).

Table 7: Grading of rocm based on code mucor.

ROCM Grade	No. of cases	%
3a	4	7.3
3b	18	32.7
3c	28	50.9
3d	1	1.8
4a	3	5.5
4b	1	1.8
Total	55	100

ROCM=Rhinoorbital Cerebral Mucormycosis

Management and outcome ROCM

- Primary initiations of medical management with injection Amphotericin-B was preferred in 76.4% and during the shortage of injection Amphotericin-B, tablet Posaconazole (69.1%) and Itraconazole (21.8%) were started. Injection Amphotericin-B was started before surgery and continued for 10-15 days postoperatively. Following the cessation of injection Amphotericin-B, patients were started with oral Posaconazole in 67.3% of cases. Transcutaneous retrobulbar amphotericin-B injection was given through medial canthus in 74.5% of patients for 7 days. In all, 40% underwent Functional Endoscopic Sinus Surgery (FESS), nasal swab was sent of all 40 patients for histopathology and tissue invasion of hyphae consistent morphologically with mucor were seen in all 40 patients. FESS with orbital debridement was done in 32.7% and exenteration was done in 1.8%.
- Among all, 67.3% were alive with clinic or radiologically stable ROCM and well with regression of ROCM at the time of discharge from the hospital. In ocular outcome, improvement of ptosis and extra ocular movements was noted in patients who were treated with injection Amphotericin-B and TRAM during the early stages in the course of the disease like in stage 3a and 3b (18.18%). Vision was salvaged (vision better than CF3 meters) in 15 (27.27%) cases. Patients with the involvement of orbital apex and superior orbital fissure, vision could not be salvaged in 22 (27.27%) cases and progressed to optic atrophy. In all, 20% of Patients were referred to higher center and mortality was seen in 12.7% (Table 8).

Table 8: Treatment received and condition of the patients at the time of discharge.

Treatment	No. of cases	%	
Antifungal	Inj.AMP	42	76.4
	Tab POSACO	38	69.1
	Tab ITRACO	12	21.8

TRAMB		41	74.5
FESS	FESS	40	72.7
	FESS+OD	18	32.7
Exentration	INDICATED	29	52.7
	DONE	1	1.8
Outcome			
IM		37	67.3
Death		7	12.7
RHC		11	20
Total		55	100

Note: Inj.AMP=Injection Amphotericin-B; Tab POSACO=Tablet Posaconazole; Tab ITRACO=Tablet; Itraconazole, TRAMB=Transcutaneous Retro Bulbar Amphotericin-B, Itraconazole; IM- Improved, RHC=Referred to Higher Center; TRAMB=Transcutaneous retrobulbar Amphotericin-B

DISCUSSION

- During the pandemic of COVID 19 in 2021, the surge of mucormycosis in India is alarming due the extensive number of cases, high mortality and limited number of antifungal drugs. The crisis of mucormycosis was further worsened due to scarcity of amphotericin B caused by the large number of mucormycosis [6]. An early diagnosis with prompt, well-coordinated, multidisciplinary approach has been vital to save life and sight of the patient.
- We included total of 55 cases of rhino-orbital-cerebral mucormycosis reported to our hospital from May to July 2021.
- The mean age of patients in our study was 51 ± 11.3 years with wide range being 28-80 years with 72.7% of male predominance. Similarly, in the study by Mrittikasen, et al., the mean age was 51.9 years with 71% of male patients [7]. Thus the demographic profile of our patients was consistent with various studies. Greater outdoor exposure and, therefore, to fungal spores and increased prevalence of diabetes mellitus in males may be the possible reason for the male predominance.
- Among the total sample size most of the patients that is 50.9% presented to mucormycosis ward with signs and symptoms of mucormycosis, among whom 34.5% had previous history of COVID-19 and 16.4% had no history of COVID-19 in the past. 32.7% of people presented to COVID ward with signs and symptoms of COVID-19 among whom few developed mucormycosis eventually and few of them had simultaneously mucormycosis as well. Though majority of the population

presented with symptoms of mucormycosis rest of them presented with signs and symptoms of COVID-19 who eventually developed mucormycosis thus signifying the need to be vigilant to diagnose it. Ours is an only study to the best of known commenting on the presentation of the patients to the respective wards based on their signs and symptoms.

- The probable predisposing factors for the development of infection was, concurrent ongoing COVID 19 positivity at the time of admission (49.1%), past history of COVID 19 was present in 34.5%. In the study by Swati, et al., the concurrent on going COVID-19 was present in 61.2% and it was 62.7% which was higher compared to our study.
- The mean duration of diagnosis of COVID 19 and development of symptoms of mucormycosis was 11.21 ± 8.41 days (range: 1.0-30.0), similar to Mrittika Sen, et al., the mean interval of the onset of symptoms of ROCM from the diagnosis of COVID-19 was 14.5 ± 10 days, which was comparable to our study. As number of our patients developed symptoms of mucormycosis after recovering from COVID-19 usually between second and third week, follow up of high risk patients with COVID-19 for sequelae is important.
- Treatment with steroid during the course of COVID 19 was present in 45 (81.81%) patients. Mean duration of steroid given was 8.39 ± 2.5 days (range: 3.0-15.0 days). Steroid history of 6 patients during the course of COVID 19 could not be elicited. This was similar to a study by Mrittikasen, et al., usage of steroid was seen in 87% with mean duration of

oral steroid usage was 8 days. This shows that use of corticosteroids was the commonest risk factor. The COVID-19 positivity and concurrent steroid use further decreases the immunity. This correlation has been studied in various studies [8-12]. Marked reduction in CD4T and CD8T caused by SARS-CoV-2 lowers the defense against invasive fungal infection, attenuated phagocytic activity of leukocytes due to immunosuppression by the virus itself and the corticosteroids used in the management. A large number of ROCM cases presenting during second wave similar to our study may indirectly point towards the new viral variant in ROCM.

- In our study 80% were diabetic of which 47.3% were known case of DM and 32.7% was newly diagnosed diabetic. This was consistent with the study by Ritu Arora, et al, where 81.6% were known diabetic and 16.6% were newly diagnosed diabetic. Diabetes is one of the major independent risk factor making the host susceptible to infections by mucorales as seen in various studies. Due to increased glycosylation, IL-10 production by lymphocytes and macrophages is significantly reduced, also reduces polymorph nuclear leukocyte mobilization and chemotaxis. Phagocytic cell dysfunction induced by hyperglycemia and acidosis lead to increased risk of Mucorales infection.

Symptoms, signs and site of involvement in ROCM

- The commonest symptom/sign of rhinoorbital mucormycosis was proptosis (65.5%), partial ophthalmoplegia (36.5%), ptosis (50.9%), total ophthalmoplegia (53.5%) and loss of vision (18.2%). Few had CRAO, CRVO and retinitis similar to study by Nurettin Bayram, et al, the commonest symptom and signs were proptosis (100%), ophthalmoplegia (63.6%), ptosis (63.6%) and decreased vision in 27.3%.
- In all, 34.55% of cases involved orbital apex at the time of presentation, 25.45% involved diffuse periorbital tissue and cavernous sinus was involved in 7.27%.
- Due to maximum number of patients in stage 3c (50.9%), indicates the need for high index of suspicion in COVID-19 and diabetes patients. This is in consistence with Ritu, et al. where the presentation of 58.3% cases were beyond stage 2 ROCM. This indicates the high index of suspicion of spread of mucormycosis from nasal mucosa probably periosteum to the orbital apex and superior orbital fissure in the initial stage of orbital involvement.

Management and outcome

- Among the total study population, only 76.4% have received intravenous injection Amphotericin B due to scarcity of the drug and rest have received tablet Posaconazol and Itraconazole. Compared to 98% and 81.9% of patients in a study by Mrittikasen, et al., amphotericin was given in less number of patients in our study. Transcutaneous retrobulbar Amphotericin B was given in 74.5% of cases. In ocular outcome, improvement of ptosis and extra ocular movements was noted in patients who were treated with injection Amphotericin-B and TRAMB during the early stages in the course of the disease like in stage 3a and 3b (18.18%). Vision was salvaged (vision better than CF3 meters) in 15 (27.27%) cases. Patients with the involvement of orbital apex and

superior orbital fissure, vision could not be salvaged in 22 (27.27%) cases and progressed to optic atrophy [13-16]. TRAMB can be considered as a viable option in selected cases of orbital mucormycosis where exenteration or debridement are not indicated, or when there is limited orbital disease to salvage the eye by avoiding exenteration as supported by various studies.

- Functional endoscopic sinus surgery was done in 72.7% and FESS with orbital debridement in 32.7% and orbital exenteration in 71.8%. Compared to study Mrittika, et al., where FESS, FESS with orbital debridement and exenteration was done in 67%, 17% and 15% respectively. Our study shows that early and prompt treatment could salvage the eye without the need for exenteration and among all 67.3% were alive with clinicoradiologically stable ROCM and well with regression of ROCM at the time of discharge from the hospital.
- In all, 20% of Patients were referred to higher center and mortality was seen in 12.7%. Prognosis was poor once the disease advanced to stage 3c or worse with mortality (7%) and 20% patients were referred to higher center due to CNS involvement. In the study by Atul Patel, et al. (38.3%), (14%) the mortality rate was higher. Compared to other studies mortality rate in our study is lesser with early and prompt initiation of treatment. Thus signifying the importance of early diagnosis and prompt treatment reducing the mortality of the patients.

CONCLUSION

In our study diabetes mellitus and steroid usage during the course of COVID-19 treatment seem to be the main factors that make patients susceptible to mucormycosis. Mucormycosis should be suspected in patients with COVID-19 irrespective of severity with history of steroid usage associated with diabetes mellitus in second and third week. Look for symptoms and signs of early involvement of orbital apex and superior orbital fissure. Our study signifies the importance of early diagnosis and prompt initiation of treatment with systemic, transcutaneous retro bulbar Amphotericin B injection and debridement of the orbit helps to salvage eye without requiring orbital exenteration. Even during scarcity of drugs and inadequately equipped health system we were still able to salvage eyes in maximum number of patients.

LIMITATIONS

As it is retrospective study follow up of the patients was not done.

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