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COVID 19 Associated Rhino-Orbital-Cerebral Mucormycosis- Clinicoetiological Profile and Management Outcome of Patients in Tertiary Eye Care Centre in Northern India

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Abstract

Purpose: To analyse demographic data, clinical presentation, intervention and management of Post COVID 19 Rhino-orbito-cerebral- mucormycosis (ROCM) thus improving the knowledge about the disease to provide timely and optimal care for favorable outcome. ***Method:*** A retrospective interventional study was conducted on 254 patients admitted in Mucor ward over a duration of 2 months (1st May 2021- 30th June 2021). Demographic data, detailed history, clinical parameters, diagnostic procedures, management and outcome were noted. Factors affecting outcome and mortality were analysed. ***Results***: Mean age of presentation was 50.14 ±13.38 years with male preponderance (64.56%). 55.91% patients presented with ROCM symptoms within 14 days of onset of COVID -19 symptoms. 86% patients were diabetics, 76% had history of corticosteroid use and 27.55% received oxygen therapy. 40 % patients presented with orbital edema as primary symptom. Imaging revealed 28.34% patients had disease limited to the paranasal sinuses (PNS), 56.69% had orbit and PNS involvement and 12.99% had PNS, orbit and CNS involvement. All the patients were treated with Liposomal Amphotericin B and sinus debridement. Eighteen eyes underwent (7.08%) exenteration and 82 patients received Transcutaneous retrobulbar Amphotericin-B. At the time of discharge the final outcome of being alive and having stable disease was found to be significant in stage 2 patients with involvement of PNS and orbit. ***Conclusion:*** Awareness of red flag symptoms and signs, high index of clinical suspicion, prompt diagnosis, and early initiation of treatment with Amphotericin B, aggressive surgical debridement of the PNS, and orbital exenteration, where indicated, are essential for successful outcome.

Keywords: COVID 19, Rhino-orbito-cerebral mucormycosis, exenteration, diabetes, steroids.

INTRODUCTION

India has recently tackled a furious second wave of COVID-19. This second wave of COVID 19 in the Asian countries especially India has unleashed the threat of one of the obscure but debilitating condition of ROCM. It is an infection of the involved tissues by the fungus Mucor of the class Phycomycetes (order Mucorales). It has been described classically as an aggressive opportunistic infection occurring in the immune-compromised patients [1]. Many theories have emerged to associate causality of ROCM with COVID infection such as immunosuppression caused by virus, corticosteroid administration, uncontrolled diabetes mellitus, and possible peripheral microthrombi. It had gripped the nation to an extent that it was itself declared an epidemic in May 2021. Review of existing literature shows that India contributed to 81% of the cases of COVID-19-associated ROCM [2].

Various states of India bore the wrath of this deadly fungus namely Gujarat, Maharashtra, Karnataka, Madhya Pradesh and followed by Haryana [3]. Fig 1 shows the census of Haryana as regards mucor patients in the State and the death toll due to it. Haryana was one of the first state to declare it as a notifiable disease on 15th May, 2021.

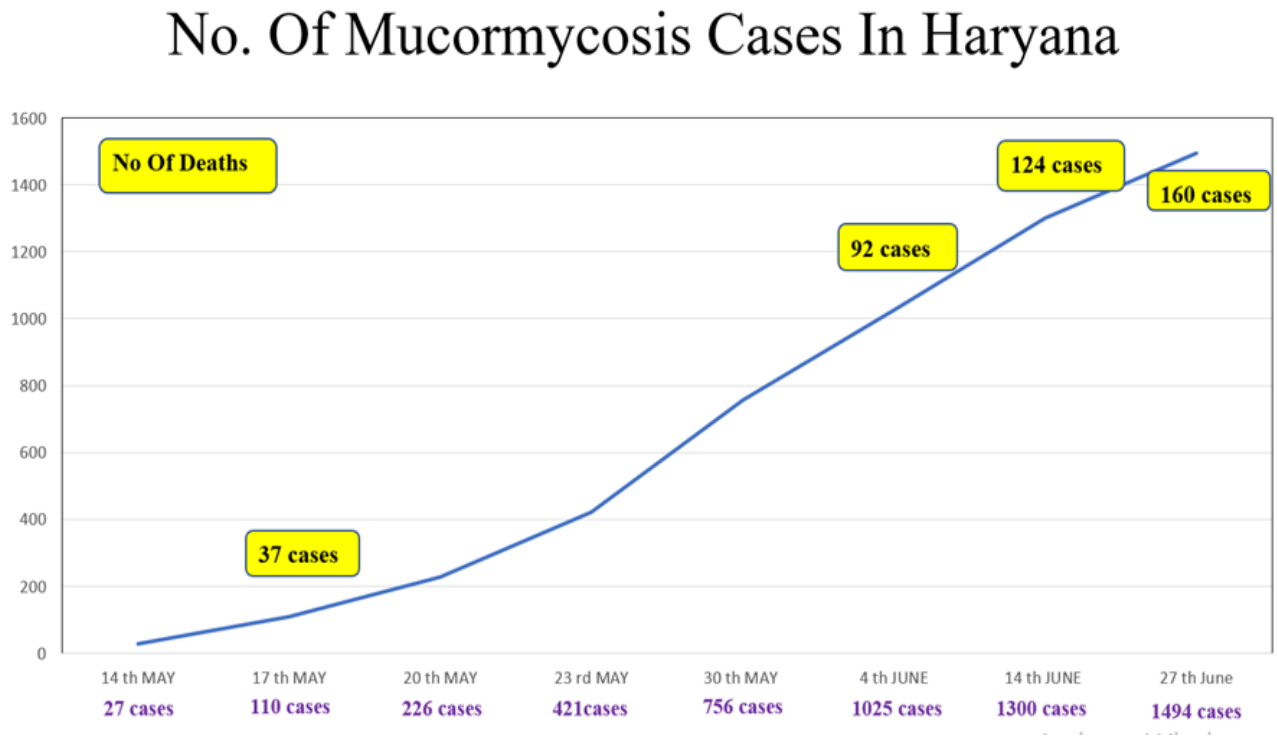

Fig 1: Census of Mucor patients in Haryana and the death toll at different time (May- June 2021)

(Source: https://www.mygov.in/information/covid-19)

METHODS

The study was carried out on patients (n = 254) admitted in dedicated mucor wards of our tertiary hospital in Haryana between 1st May 2021 to 30th June 2021. It is an interventional, institutional cohort study of patients with ROCM and concurrent or past history of COVID-19 infection. The diagnosis of COVID-19 was based on any one of the following: reverse transcription polymerase chain reaction (RT-PCR) test on nasopharyngeal or oropharyngeal swabs, rapid antigen test, or CT chest scores in the absence of a positive RT-PCR test in a clinically symptomatic case.

A detailed history was recorded at the time of admission which included presenting symptoms, timeline of the onset of symptoms of ROCM from the diagnosis of COVID-19, any history of co morbidities. Treatment received during Covid and if the patient was managed at home or hospital facilities. The patients with non-COVID-19-associated ROCM or those with proven non-mucor fungal infections were excluded from the study. Patients were defined as recovered from COVID-19 if they were tested negative on a repeat RT-PCR or if two weeks had elapsed since the diagnosis. Following detailed history all patients were subjected to clinical examination, radiological evaluation with CT PNS and gadolinium enhanced MRI brain and orbit, diagnostic nasal endoscopy and guided nasal smear /biopsy for potassium hydroxide and ophthalmology evaluation. The patients were managed via a multidisciplinary approach in coordination with ENT, Ophthalmology, Medicine, Neurosurgery, Anaesthesia, Radiology and Microbiology teams.

A working staging system had been proposed to help triage these patients and customize their care. The system is simple and follows the general anatomical progression of ROCM from the point of entry i.e. Stage 1 nasal mucosa on to Stage 2 the paranasal sinus (PNS), Stage 3 involvement of PNS + orbit, and Stage 4 Inolvement of PNS + Orbit + the central nervous system (CNS), and severity in each of these anatomical locations. In this study, all the patients were retrospectively classified into the proposed staging system [4].

RESULTS

Demographics

Age

The study population included 254 patients with age group ranging from 20 years to > 80 years. 46.85% (119) of patient were in the age group 41-60yrs. The mean age of the study population was 50.14 ±13.38 years. Fig 2 summarises the age wise distribution of patients under study.

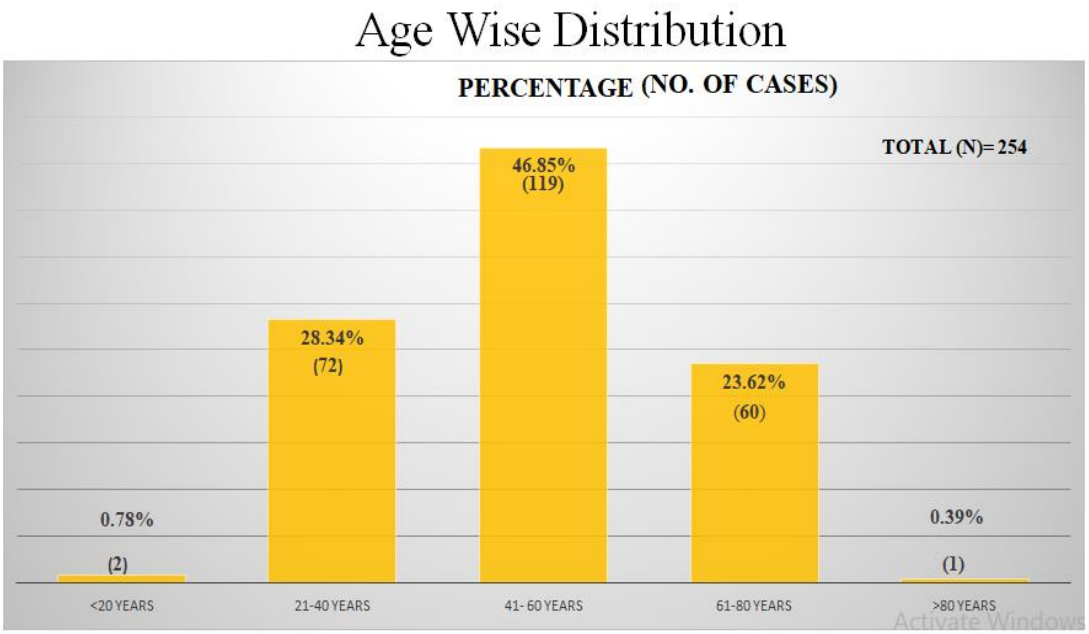

Fig 2: Age wise distribution of patients

Gender

Male to female sex ratio was 10.8:1 with 64.56% (164/254) patients being males. Fig 3 summarises the Gender distribution of patients and depicts a visible male preponderance among the patients.

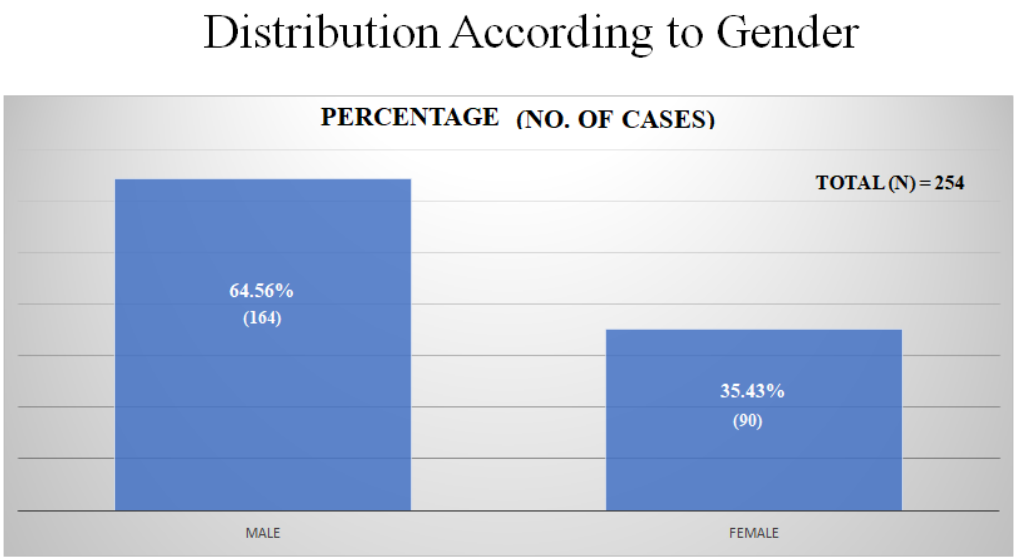

Fig 3: Gender distribution of patients

Potential risk factors for COVID-19 associated ROCM

Fig 4 shows that RTPCR status was positive in 52% cases (133 patients), while it was negative in 41% (121 patients). The difference being insignificant. It summarizes that RTPCR status is a non-specific criteria for disease assessment. Clinical symptoms of COVID illness correlate with the mucor status more than the RTPCR status.

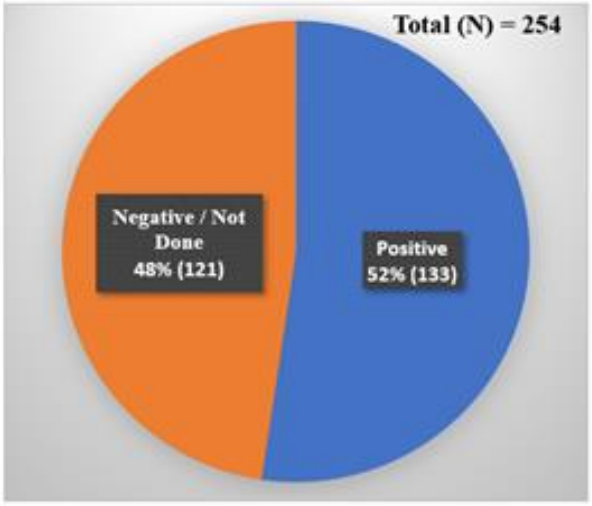

Fig 4: RTPCR status of patients during COVID illness

Table 1: Data of Potential Risk Factors

HISTORY	PERCENTAGE (NO. OF CASES / TOTAL NO. OF CASES)
HOSPITALISATION	
• PRESENT	35.03% (89/254)
• ABSENT / HOME CARE	64.96% (165/254)
OXYGEN THERAPY	
• GIVEN	27.55% (70/254)
• NOT GIVEN	72.44% (184/254)
REMDESIVIR / TOCILIZUMAB	
• GIVEN	14.96% (38/254) / 0% (0/254)
• NOT GIVEN	85.03% (216/254) / 100% (254/254)
STEROID	
• GIVEN	76% (193/254)
• NOT GIVEN	24% (61/254)

Table 1 depicts that among 254 patients 35.03% (89/254) were hospitalized while 64.96% (165/254) were provided home care while undertaking treatment for COVID infection. Further analysis regarding treatment protocol followed for treatment of COVID infection was done. 27.55% (70/254) received oxygen in the form prong/ mask while 72.44% (184/254) did not receive oxygen in any form. Around 14.96% (38/254) received Remdesivir and none had history of Tocilizumab.

Systemic corticosteroids (either oral or intravenous or both) as shown in Table 1 were used in 76% (193/254) patients, while 24% (61/254) did not receive corticosteroids in any form. Steroids were used for minimum duration of 10 – 12 days. Steroids were the most common risk factor and their use increased in proportion to the severity of COVID- 19. Even patients who were home cared received corticosteroids.

Table 1 suggests that the use of corticosteroids was the commonest risk factor and their use increased in proportion to the severity of COVID-19.On the other hand contaminated Oxygen/Remdesivir/Tocilizumab may not be the driver of infection.

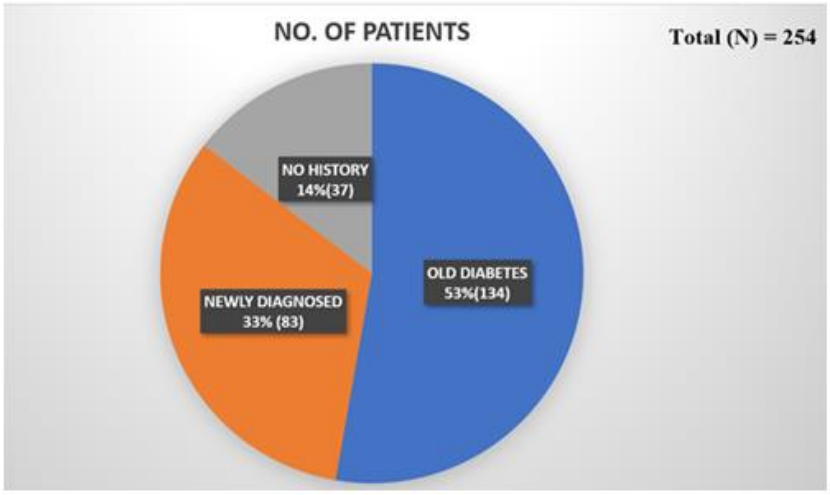

Fig 5: Status of Diabetes mellitus (DM) in mucor cases (OLD+NEW: 217cases/86%)

Among systemic comorbidities, DM status, irrespective of control, and being old or new emerged as the major risk factor. Fig 5 shows that in our study 86% (217/254) presented with diabetes. Out of which 33% (83/254) were newly diagnosed diabetics and 53% (134/254) were old cases of diabetes. 14% (37/254) of patients had no history of diabetes.

Clinical presentation of COVID-19-associated ROCM

The various clinical factors were taken up and studied one by one. These included time of onset of symptoms post COVID, the primary symptoms and signs at presentation, vision at presentation and retinal assessment.

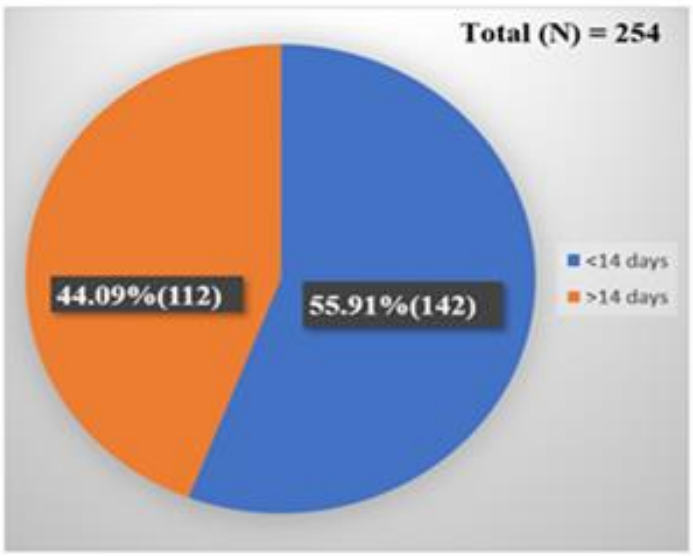

Fig 6: Duration Post COVID at primary symptom presentation

The timeline of the onset of symptoms of ROCM was enquired. All patients admitted in mucor wards were POST COVID. The range of duration being 5 days Post Covid to 3 mths Post Covid. Fig 6 shows that while 55.91% (142/254) of patients presented within 14 days of having COVID infection the remaining 44.09% of patients showed a delayed presentation beyond 14 days. Hence making follow-up of patients necessary for a period of at least three months Post COVID and keeping a high index of suspicion throughout

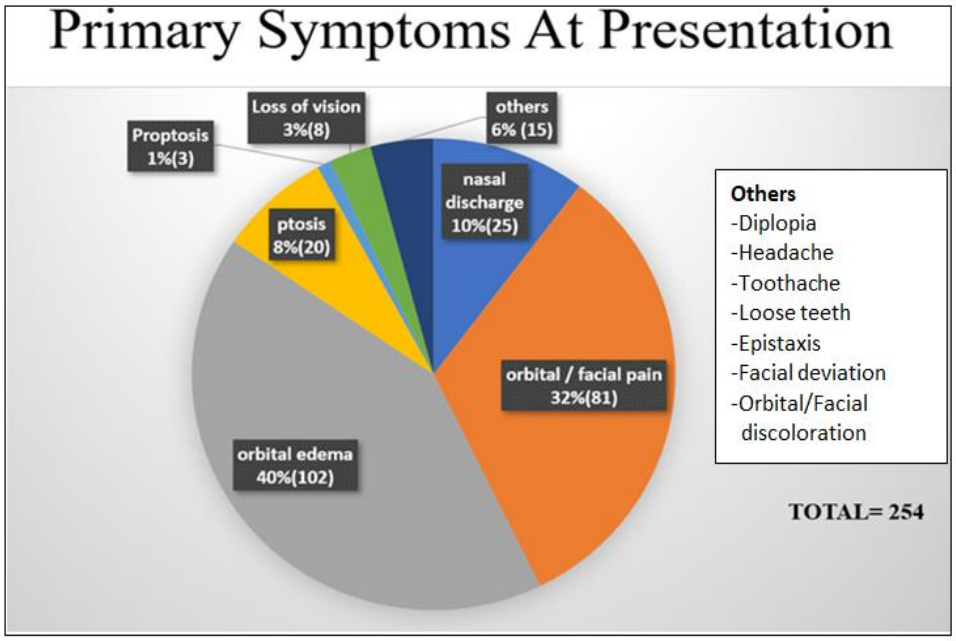

Fig 7: Frequency of the most common primary symptoms of ROCM at presentation

In our study, of all the symptoms with which the patient presented, orbital edema was present in 40% (102/254) patients as shown in Fig 7. Next common primary symptom noticed was orbital/facial pain 32% (81/254). Other symptoms were nasal discharge 10% (25/254), ptosis 8% (20/254), loss of vision 3% (8/254), proptosis 1% (3/254) and others 6%, (15/254).

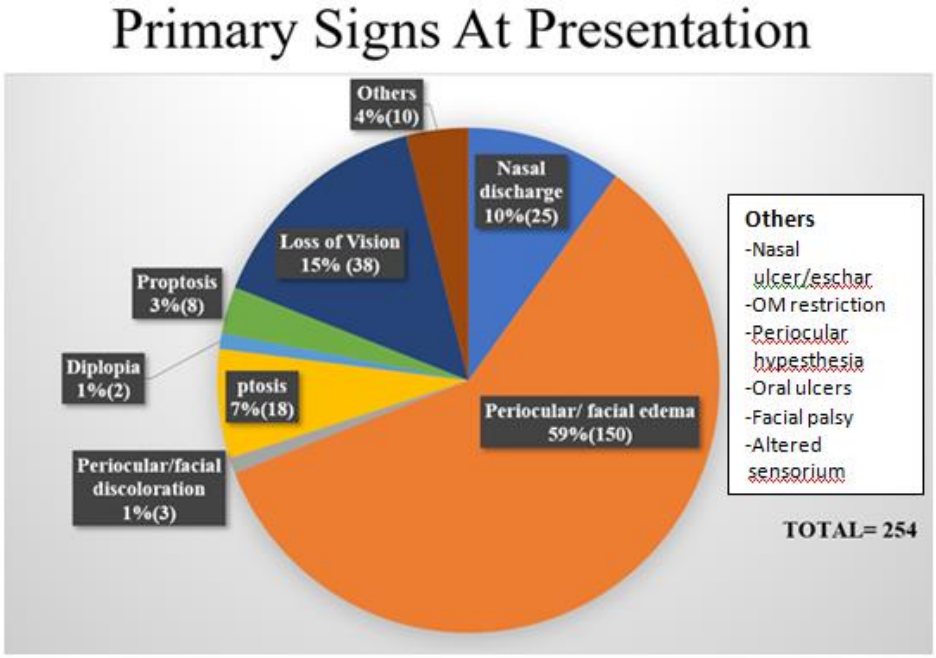

Fig 8: Frequency of the most common primary signs of ROCM at presentation

The most common primary sign at presentation as shown in Fig.8 was Periocular/ facial edema 59%(150/254).Other primary signs included Loss of Vision 15% (38/254), Nasal discharge 10% (25/254), ptosis 7%(18/254), other signs like nasal ulcer, periocular facial hypoesthesia, oral or palatal ulcer, facial palsy were seen in 4%(10/254), while proptosis presented in 3%(8/254), diplopia and periocular discoloration in 1%(3/254) each.

P. S. Permission to share pictures for academic purposes was taken from patients.

Initial presentation

Fig 9.1: Varied Presentations of ROCM Patients

Ophthalmoplegia

Fig 9.2: Varied Presentations of ROCM Patients

Moderately Aggressive

Fig 9.3: Varied Presentations of ROCM Patients

Mild to moderate OM restriction to a Frozen globe

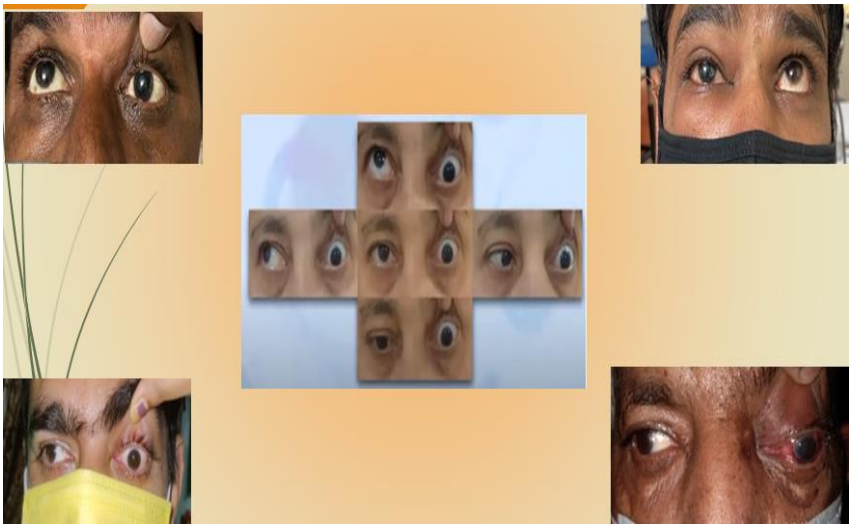

Fig 9.4: Varied Presentations of ROCM Patients

Eschar formation

Fig 9.5: Varied Presentations of ROCM Patients

Extremely aggressive

Fig 9.6: Varied Presentations of ROCM Patients

Table 3: Vision at Presentation

Vision	No of Cases (%)
PL Negative	56 (22.04%)
6/36 - PL Positive	102 (40.15%)
6/24 – 6/12	58 (22.83%)
>6/12	38 (14.96%)

Visual Assessment

The vision of patients was assessed on presentation. As shown in Table 2.the maximum patients (40.15% i.e.102/254 patients) were having vision in the range of 6/36 – PL Positive. The cause of loss of vision was studied in patients. Most of them showed orbital apex involvement leading to optic nerve damage and also 3rd, 4th, 6th nerve palsy leading to frozen globe. Retinal Assessment showed – Central Retinal Artery Occlusion, Optic disc pallor, CRVO, BRVO, Diabetic Retinopathy. The severity of vision loss correlated well with the severity of disease.

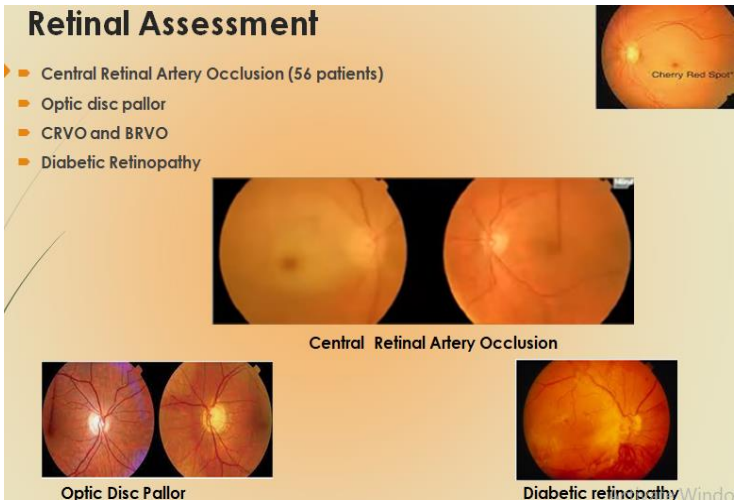

Fig 10: CRAO was the commonest presentation in patients with vision loss

Diagnosis of COVID-19-associated ROCM

Diagnostic nasal endoscopy was performed by the ENT team in all the patients at their presentation. Microbiological evidence was collected – direct microscopy with KOH/calcofluor white and as smear reports.

CT PNS was the investigation of choice for each patient on presentation. With the report of CT PNS showing involvement of nasal mucosa and paranasal sinuses the patients were admitted in the wards. On admission the patients were advised to get baseline heamatological investigations which specifically included blood urea and serum creatinine. In patients with normal KFT Contrast enhanced MRI of orbit and brain was done for assessing the orbital and intracranial spread of disease, while a plain MRI orbit and brain was done in patients with deranged KFT reports.

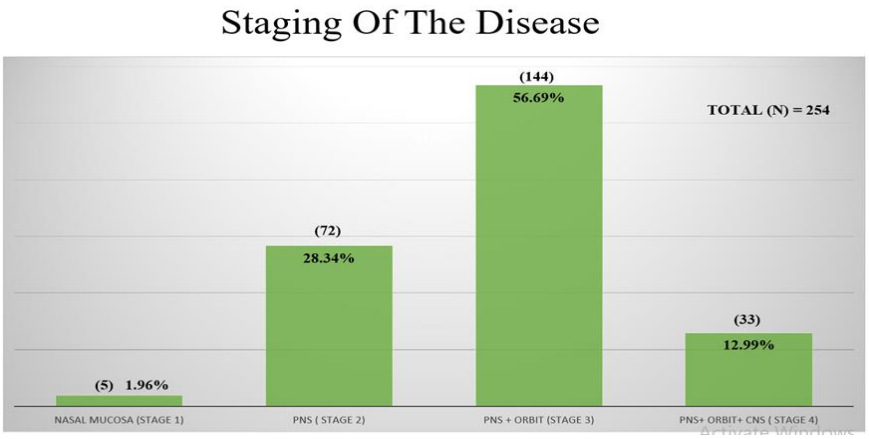

Fig 11: Staging of Disease of ROCM patients

Fig 11 summarises Staging of ROCM done based on the available information in 254 patients. Out of 254 patients, 1.96% (5/254) patients were grouped in Stage 1 i.e. they showed involvement of nasal mucosa only. 28.34% (72/254) patients belonged to Stage 2 i.e. involvement of paranasal sinuses alongwith nasal mucosa. Maximum number i.e. 56.69% (144/254) of patients were grouped in Stage 3 i.e. PNS+Orbital involvement. 12.99% (33/254) patients were categorized as Stage 4 i.e PNS+ Orbit+ CNS involvement.

Management of COVID-19-associated ROCM

Primary initiation of medical management with intravenous Liposomal Amphotericin B was preferred in all the patients as soon as it could be made available. The recommended dosage was 5mg/KBW to 10mg/KBW (Based on staging). Surgical intervention also had to be done in all patients to clear the fungus load.

FESS surgery (Functional endoscopic sinus surgery) or endoscopic debridement was done by the ENT team as the primary procedure in 221 patients. FESS + Exenteration was done in 18 patients who showed extensive involvement of orbit and also threat of spread to the CNS. Maxillectomy and other dental interventions were also done in patients wherever needed.

A new modality of treatment was also added in patients wherever required. Transcutaneous retrobulbar Amphotericin B injection (TRAMB) in the dose of 3.5mg /ml was given initially in patients with some vision in their eye. 5 to 7 injections were given preferably in the superomedial quadrant of the eye on daily basis or alternate days in case the injection caused any chemosis in the eye. Finding improvement in vision in few patients and decreased pain, headache and periorbital oedema in a number of patients the injection was also started in patients with visual status of No perception of light.

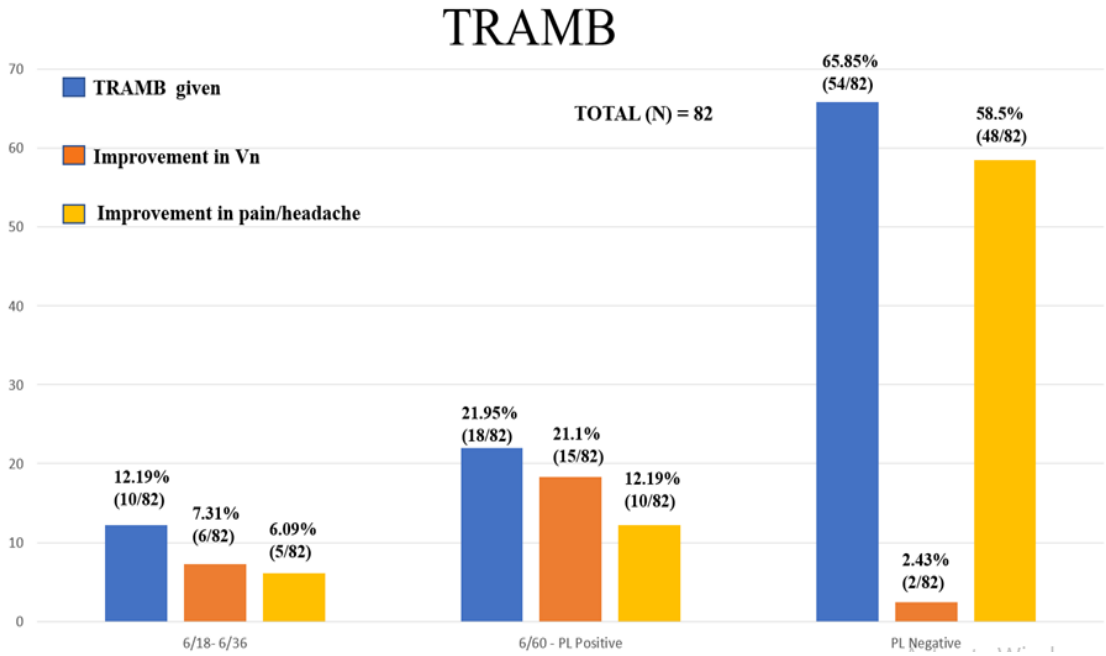

Fig 12: Data of patients given TRAMB. Summarises the positive results seen in patients given Inj.TRAMB

Out of 254 patients 82 patients were given TRAMB injection. The effect of TRAMB was graded on the basis of improvement in vision and also improveement in symptoms of pain and headache.

In 12.19% (10/82)patients given TRAMB the vision at presentation was in the range of 6/18 – 6/36.After 3 to 4 TRAMB inj. 7.31%(6/82)patients showed one to two lines of visual improvement, while 6.09%(5/82)patients in this group showed improvement in pain/headache.

In 21.95% (18/82) patients given TRAMB the vision at presentation was in the range of 6/60 – PL positive. After 3 to 4 TRAMB inj. 21.1%(15/82) patients showed one to two lines of visual improvement, while 12.19%(10/82) patients in this group showed improvement in pain/headache.

In maximum patients i.e 65.85%(18/82) patients given TRAMB the vision at presentation was PL negative. After 3 to 4 TRAMB inj. 2.43 %(2/82) patients showed one to two lines of visual improvement, while 58.5%(10/82) patients in this group showed improvement in pain/headache.

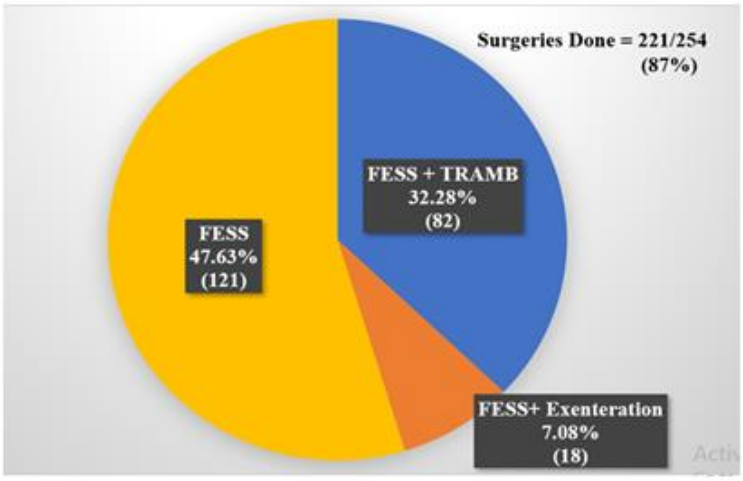

Fig 13: Various treatment modalities followed (Surgeries done till 30/6/21)

Fig 13 summarises the various modes of treatment which had to be overlapped in patients for improved outcome. While in 47.63% (12 patients) only FESS was needed the remaining 32.28%(82/254) patients TRAMB had to be added. Unfortunately in 7.08% (18) patients FESS had to be accompanied with Exenteration as a life savving procedure after taking informed consent from them.

Outcome of COVID-19-associated ROCM

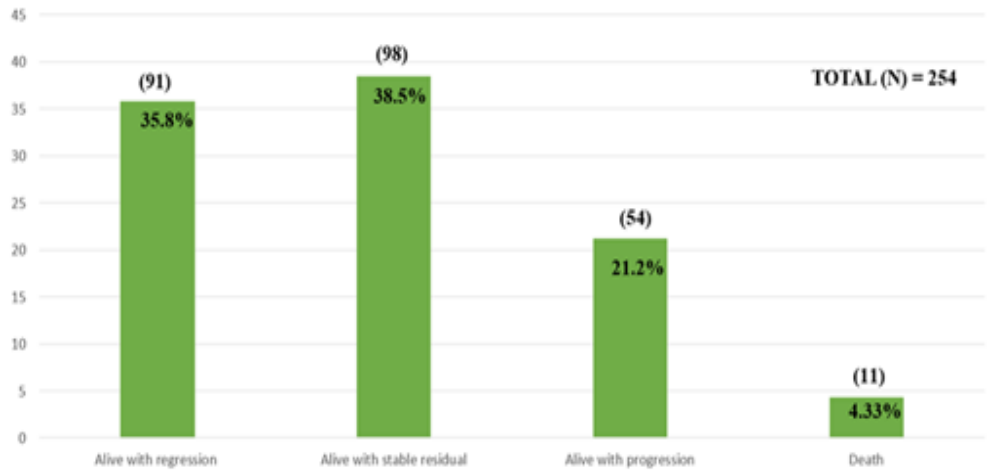

Fig 14: Summarises the outcome of patients assessed as on 30th June, 2021

Outcome of treatment in mucor patients

The first batch of 10 patients who had completed their course of Amphotericin B were discharged on step down treatment with Tab. Posaconazole and since then daily 10 to 15 patients were being discharged with a follow up to be done after 1 week.

Among the ones alive, ocular outcome was available for all the patients, 18/254 patients (7.08%) had orbital exenteration and in remaining 236/254 patients (92.9%) the eye could be salvaged. Out of these 236 patients 54 patients had turned PL Negative in the involved eye while 4 patients had turned bilaterally blind due to this deadly fungus.

DISCUSSION

Mucor, the ubiquitous, naturally occurring fungus is potentially lethal,causing an angioinvasive fungal infection predisposed by diabetes mellitus, corticosteroids and immunosuppressive drugs, primary or secondary immunodeficiency, hematological malignancies and hematological stem cell transplantation, solid organ malignancies and solid organ transplantation, iron overload, etc [5].

During the second wave of the COVID -19 disease secondary infection from Mucor became rampant. The prevalence of the disease in pre covid times has been estimated to be 0.005-1.7 per million population worldwide. The prevalence in India has always been much higher, nearly 80 times that in other

parts of the world, 0.14 per 1000 [2, 6, 7]. India also occupies the second position in the world as far as the number of diabetics is concerned [8].

The possible reason for the high prevalence is the abundant presence of Mucorales in the community and hospital environment, large number of susceptible hosts especially diabetics, and the neglect for regular health check-ups of Indian population.

In the Indian population, the mean age of COVID-19 patients admitted to a hospital was 45–50.7 years and 56–93% of the patients were males [9, 11]. The demographic profile in our study is consistent with these studies with mean age 49.94 years and male preponderance (64.56%,). This male preponderance can be associated with greater outdoor exposure and, therefore, to fungal spores.

Corticosteroids have been considered culprit for their role in increasing the susceptibility to mucormycosis and the allegation seems quite right. Prolonged, >3 weeks of high-dose systemic corticosteroid has been implicated as a risk factor for mucormycosis in non-COVID-19 patients [12]. According to the published literature, 76% of the patients with COVID-19-associated ROCM gave history of systemic corticosteroids [2]. In India, this fraction is higher i.e. 88% [13]. Our data revealed that systemic corticosteroids had been used in 76% of the patients. Thus, irrational or injudicious use of corticosteroids can be a possible cause of ROCM.

DM has been identified as an independent risk factor for mucormycosis [14]. In a large series of cases from India of mucormycosis in the pre-COVID-19 era, 74% of the patients were diabetics [15]. The risk of mucormycosis is 7.5 times higher in diabetics than the general population [16]. On looking at the current scenario of COVID-19-associated ROCM in India, in a study of 41 cases by John *et al*., [17] 93% were diabetics. Our data showed similar results, but we did not differentiate between type 1 and type 2. Our study also reports 86% patient to be diabetic out of which 33% had new onset diabetes.

ROCM can occur both concomitantly with COVID-19 as well as post recovery till 3mths as seen in our study. It can have varied presentation. The red flag signs as shown in Table 4 and these should be known by all physician so that early diagnosis and treatment can be administered. Educating the patients and families with a checklist of symptoms, mucor helplines, and follow-up clinics for COVID-19 recovered patients are possible solutions.

Table 4: Warning symptoms and signs of rhino-orbito-cerebral mucormycosis [4]

• Nasal stuffiness
• Foul smell
• Epistaxis
• Nasal discharge - mucoid, purulent, blood-tinged or black
• Nasal mucosal erythema, inflammation, purple or blue discoloration, white ulcer, ischemia, or eschar
• Eyelid, periocular or facial edema
• Eyelid, periocular, facial discoloration
• Regional pain – orbit, paranasal sinus or dental pain
• Facial pain
• Worsening headache
• Proptosis
• Sudden loss of vision
• Facial paresthesia, anesthesia
• Sudden ptosis
• Ocular motility restriction, diplopia
• Facial palsy
• Fever, altered sensorium, paralysis, focal seizures

Amphotericin B is the antifungal drug of choice for mucormycosis. It has been used in 88% of the patients of COVID-19-associated ROCM [18]. Induction should be in full dose (5 mg/kg body weight for stages 1–3 and up to 10 mg/body weight for stages 4) with liposomal amphotericin B. If not available, one can use amphotericin B deoxycholate or amphotericin B lipid complex. The liposomal form is preferred since it is less nephrotoxic. Our data shows that efforts were made to provide liposomal form to all admitted patients. Some patients received both the liposomal and deoxycholate type because of logistic reasons.

Prolonged long term step down oral therapy is warranted for 3-6 months [19-21]. Isavuconazole and Posaconazole are two drugs that can be used for this purpose. A study from India has shown posaconazole to be highly effective as salvage therapy for ROCM with life salvage and complete resolution in 67% of the patients [22]. In our study, all patients in the process of

being discharged are being advised posaconazole therapy.

Intraorbital injection of Amphotericin B deoxycholate can be used as an adjunct to surgical and medical management. It has been shown to be effective for life and eye salvage in certain case reports [23-25] and is being increasingly used despite paucity of literature. Our patients also showed positive results with use of it.

PNS debridemnt is the primary management which serves both diagnostic and therapeutic purpose. In our study PNS debridement was done in 87% cases and FESS along with exenteration was done in 7.08% patient. Maxillectomy surgery was also needed in number of cases in our study. However, on analyzing the patients with CNS involvement it was seen that PNS debridement was associated with better outcome than with no surgical intervention at all. Thus, surgery may not be a contraindication in patients with CNS involvement and may indeed improve survival. Orbital exenteration may also play a significant role in advanced disease and help in prevention of intracranial spread leading to better prognosis in terms of survival.

CONCLUSION

COVID 19 associated ROCM majorly involves middle age and older men presenting with symptoms mainly after 10-15 days post Covid period. Diabetes mellitus and corticosteroid are potent risk factors. ROCM is rare in patients devoid of the risk factors. It needs to be tackled as aggressively as the disease itself with a concerted effort from multidisciplinary medical teams and the government. Logistical preparedness to ensure adequate supply of amphotericin B and creation of well-equipped, dedicated regional multidisciplinary ROCM-management centres, each connected to spokes of COVID-19-treatment facilities, may help salvage the life and eyes of these patients

LIMITATION

One of the major limitation of the study is that the disease has a long course and patients need to be followed up regularly. Some of the patients are still receiving treatment and are on follow up. This study provides the data about post Covid surge of the debilitating fungus mucormycosis which can help in future for proper understanding of the disease and its management. Rehabilitation of these patients is also bein done with passing time.

ACKNOWLEDGMENTS

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