

Retinal Manifestations in Rhino-orbito-cerebral Mucormycosis: A Cross-sectional Study

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ABSTRACT

Introduction: Rhino-orbito-cerebral Mucormycosis (ROCM) is an uncommon but devastating fungal infection caused by Mucoraceae family fungi, which are angiotropic and filamentous, with significantly high morbidity and mortality despite treatment. Post Coronavirus Disease-2019 (COVID-19), there was a sudden surge in ROCM cases nationwide due to immunologically and metabolically compromised status.

Aim: To describe retinal manifestations in ROCM in a tertiary eye care centre of Northern India.

Materials and Methods: An analytic, cross-sectional and hospital-based study was conducted in Regional Institute of Ophthalmology, PGIMS Rohtak, Haryana, India, from May to September 2021. This study was conducted on 200 admitted patients of RCOM in the institute, which was only designated nodal centre in Haryana, India. Detailed history was recorded in every patient regarding presenting symptoms, history of COVID-19, hospital stay, oxygen inhalation, steroid intake and immunisation. Thorough ocular examination was done in every patient including visual acuity, ocular movements and pupillary reactions. Dilated fundus examination was done by Indirect Ophthalmoscopy (IDO) for posterior segment evaluation. Contrast Enhanced Magnetic Resonance Imaging (CE-MRI) brain with orbit and Paranasal Sinus (PNS) was done in every patient to see the extent of spread and planning further management.

Results: Out of 200 patients of ROCM, majority of patients 64 (32%) were of 51-60 year age group followed by 41-50 year

age group (28%). Out of 200 cases of ROCM, 146 patients (73%) had history of COVID-19 infection in past and 134 (67%) patients had history of hospital stay during COVID-19 infection. Oxygen (O₂) supplementation was given to 98 patients either at home or during hospital stay. History of steroid intake was present in 34 patients and 46 patients received injection remdesivir. Only 12 patients had vaccine against COVID-19 and none of them were fully vaccinated. Most common presenting symptom was unilateral nasal stiffness (22%) followed by loss of vision (17%). Most common predisposing factor was Diabetes Mellitus (DM) in 78 (39%) patients followed by steroid intake in 34 (17%) patients. Out of 200 patients, only 60 patients had retinal manifestations and most common was Central Retinal Artery Occlusion (CRAO) (35/60) and the main mechanism is the direct infiltration of central retinal artery due to angioinvasion of fungi from the orbit.

Conclusion: The CE-MRI brain with orbit is an important tool in diagnosing and monitoring progression of RCOM but it cannot provide information regarding retinal findings like CRAO, Central Retinal Venous Occlusion (CRVO), disc pallor and optic atrophy. Thus, the fundus examination of every ROCM patient should be emphasised, as it not only helps in categorising ROCM but also tells about the visual potential of affected eye. Patients with CRAO and combined vascular occlusion should be considered for exenteration on urgent basis, so that intracranial spread can be prevented and patient's life can be saved.

Keywords: Coronavirus disease-2019, Central retinal artery occlusion, Mucorales infection, Retinal vein occlusions

INTRODUCTION

In late 2019, multiple pneumonia cases were observed in Wuhan in Hubei province in China; caused by Severe Acute Respiratory Syndrome Coronavirus-2 (SARS-CoV-2); also known as 2019 novel Coronavirus (2019-nCoV), which is highly transmissible [1,2]. COVID-19 outbreak has affected millions globally, leading to the World Health Organisation (WHO) declaring it as a global pandemic [3]. In post COVID-19 recovery patients, there was sudden surge in ROCM cases nationwide, due to the immunologically and metabolically compromised status of these patients. A complex interplay of factors i.e., pre-existing DM, previous respiratory pathology, use of immunosuppressive therapy, prolonged hospitalisation and intensive care, oxygen supplementation, iron overload, direct cytopathological effects of virus and systemic immune alteration of COVID-19 infection may lead to secondary bacterial and fungal infections [4].

The ROCM is a rare, but devastating opportunistic fungal infection caused by angiotropic filamentous fungi of Mucoraceae family with significantly high morbidity and mortality. These fungi are angioinvasive in nature due to its predilection for the internal elastic

lamina of blood vessels leading to thrombosis and haemorrhagic necrosis. Sinus infection spreads into the orbit and brain due to the same mechanism, leading to a spectrum of RCOM [5].

Mucormycosis is a fungal infection caused by a group of angioinvasive saprophytic fungi, which include the genera *Rhizopus*, *Mucor* and *Absidia*. These fungi are ubiquitous and saprophytic, which are found in fruits, dust, soil and manure and can be cultured from the nasal mucosa of healthy individuals [6,7]. The presence of debilitating diseases and compromised host defence allows the sporulation and growth of these fungi. The predisposing factors for ROCM are uncontrolled DM complicated by Diabetic Ketoacidosis (DKA), organ transplant recipients who are on immunosuppressants, patients on any steroid or cytotoxic therapy, leukaemia patients and other disseminated cancer patients. Among all, the most common predisposing factor for mucormycosis is uncontrolled DM, especially if complicated by ketoacidosis. It is secondary to various reasons including the hampering of host phagocytosis and mobilisation of polymorphonuclear leukocytes, high blood glucose levels, ketoacidosis and increased free serum iron availability at low pH, all of these helps in growth of these fungi [3,8].

The route of transmission of ROCM is inhalation and it always starts in the nasal or paranasal sinus mucosae after inhalation of fungal spores and thereafter it spreads in neighbouring tissues, including orbit and brain secondary to angioinvasion. Early symptoms of ROCM are unilateral nasal stiffness, facial numbness, retro-orbital pain, headache and fever. If patient presents at an early stage of mucormycosis, anterior rhinoscopy may reveal a black and necrotic turbinate or septum secondary to tissue infarction. Orbital involvement may manifest as chemosis, ophthalmoplegia [Table/Fig-1a], infraorbital paraesthesia, black eschar over periorbital area [Table/Fig-1b], proptosis, diplopia, loss of vision and orbital cellulitis [Table/Fig-1c] [9]. Intracranial spread may occur via many routes including superior orbital fissure, ophthalmic vessels, cribriform plate and perineural route. Clinically central nervous system involvement manifests as altered sensorium, hemiparesis, brain abscess and meningeal signs [10].



[Table/Fig-1]: a) Early ROCM presenting as left side ptosis and complete ophthalmoplegia; b) Late stage of ROCM presenting as black eschar over left side of face; c) Late stage of ROCM presenting as orbital cellulitis (Detailed informed consent was taken from patients for publication purpose).

The present study was conducted to describe the retinal manifestations in ROCM cases in a tertiary care referral centre of Northern India.

MATERIALS AND METHODS

An analytic, cross-sectional and hospital-based study was conducted in Regional Institute of Ophthalmology, PGIMS Rohtak, Haryana, India, from May to September 2021. Informed consent of patients and ethical clearance from Institutional Ethics Committee, PGIMS Rohtak was obtained prior to the study. The study was conducted on 200 admitted patients of RCOM in the institute. It is the only designated nodal centre in Haryana, India.

Inclusion criteria: First consecutive 200 patients of RCOM fulfilling the inclusion criteria were included in the study after taking their informed written consent.

Exclusion criteria: Patient not willing to participate in the study and having hazy media secondary to corneal opacity or mature senile cataract which was obscuring posterior segment details were excluded from the study.

Detailed history was recorded in every patient regarding presenting symptoms, history of COVID-19, hospital stay, oxygen inhalation, steroid intake and immunisation. Thorough ocular examination was done in every patient including visual acuity, ocular movements and pupillary reactions. Detailed dilated fundus examination was done with IDO for posterior segment evaluation. CE-MRI brain with orbit and PNS was done in every patient to see the extent of spread and planning further management.

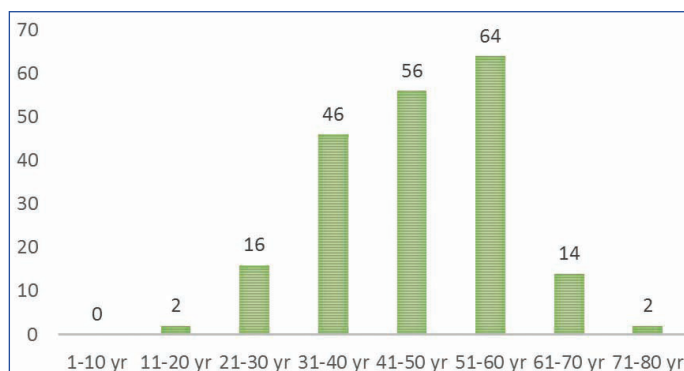
STATISTICAL ANALYSIS

Microsoft excel was used for compiling the data and the data was recorded in values and percentages.

RESULTS

Age distribution: Out of 200 patients of ROCM, majority of patients were of 51-60 year age group (32%) followed by 41-50 year age group (28%) [Table/Fig-2].

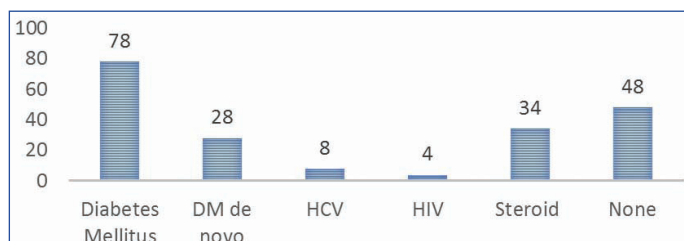
Gender distribution: In the present study, out of 200 patients of ROCM, 134 (67%) were males, while 66 (33%) were females.



[Table/Fig-2]: Age distribution of ROCM.

Detailed history was taken in every cases and out of 200 cases of ROCM, 146 patients had history of COVID-19 infection in past and 134 patients had history of hospital stay during COVID-19 infection. O₂ supplementation was given to 98 patients either at home or during hospital stay. History of steroid intake was present in 34 patients and 46 patients received injection remdesivir. Only 12 patients had vaccine against COVID-19 and none of them was fully vaccinated.

In present study, most common predisposing risk factor for ROCM was DM in (39%) followed by steroid intake (17%). About 28 (14%) patients developed diabetes mellitus after getting COVID-19 infection and were classified as DM de novo. Other risk factors were Hepatitis C Virus (HCV) and Human Immunodeficiency Virus (HIV) infection in 4% and 2% cases respectively while in 24% cases, there was no risk factor found [Table/Fig-3].



[Table/Fig-3]: Predisposing risk factors for ROCM.

In this present study, patients with ROCM presented with multiple symptoms and most common presenting symptom was unilateral nasal stiffness in 44 (22%) patients followed by loss of vision in 34 (17%) patients [Table/Fig-4].

Presenting features	N (%)
Unilateral nasal stiffness	44 (22%)
Facial numbness	28 (14%)
Headache	12 (6%)
Fever	16 (8%)
Sudden ptosis	23 (11.5%)
Sudden proptosis	16 (8%)
Loss of vision	34 (17%)
Paralysis	12 (6%)
Loosening of teeth	11 (5.5%)
Black eschar over face	1 (0.5%)
Black eschar over palate	3 (1.5%)

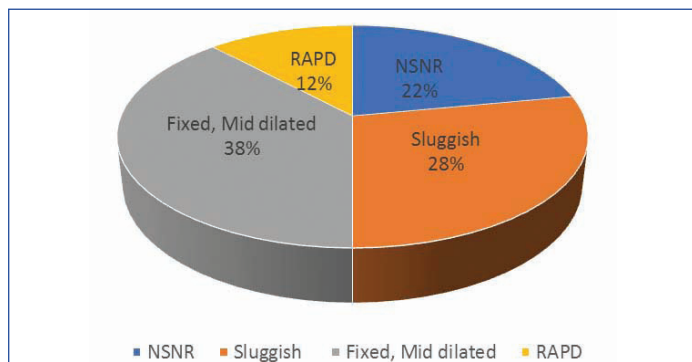
[Table/Fig-4]: Presenting manifestations of ROCM cases.

Out of 200 cases, 24 patients presented with BCVA of 6/6-6/9, 36 patients had 6/12-6/18, 44 patients had 6/24-6/36, 24 patients had 6/60, 8 had BCVA of Finger counting at 3 m-Finger counting 1 m, Finger counting close to face (FCCF)-Hand movement (HM+ve) in 12 patients, Perception of light (PL+ve) in 16 patients while 36 patients did not perceive light on presentation [Table/Fig-5].

Presenting visual acuity	N (%)
6/6-6/9	24 (12%)
6/12-6/18	36 (18%)
6/24-6/36	44 (22%)
6/60	24 (12%)
FC at 3 m-FC at 1 m	8 (4%)
FCCF-HM+ve	12 (6%)
PL +ve PR accurate	16 (8%)
PL -ve	36 (18%)

[Table/Fig-5]: Presenting VA of ROCM cases on Snellen's chart.

Out of 200 patients, pupillary reaction was essentially normal in 44 (22%) cases and Relative Afferent Pupillary Defect (RAPD) was present in 24 (12%) cases [Table/Fig-6].

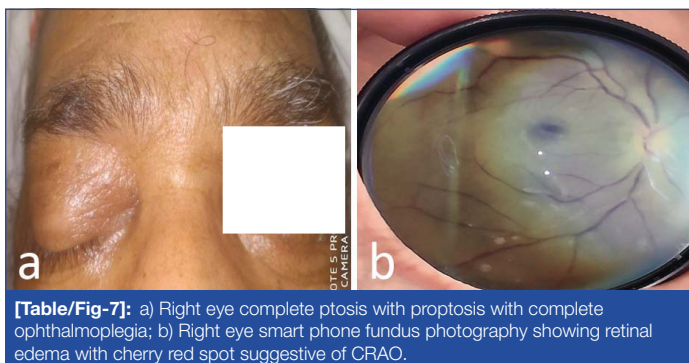


[Table/Fig-6]: Pupillary reactions in ROCM cases.

NSNR: Normal size normal reacting; RAPD: Relative afferent pupillary defect.

Ocular motility was checked in every patient in all nine gazes. Out of 200 cases of ROCM, ocular motility was normal in 78 (39%) cases, restricted in 56 (28%) cases and complete ophthalmoplegia was noticed in 66 (33%) cases.

Complete fundus examination was carried out in every patient of ROCM by IDO and smart phone fundus photography was done. Out of 200 patients of mucormycosis, only 60 patients had retinal manifestations. Fundus findings help in staging ROCM (Stage 3c if CRAO present) [Table/Fig-7].

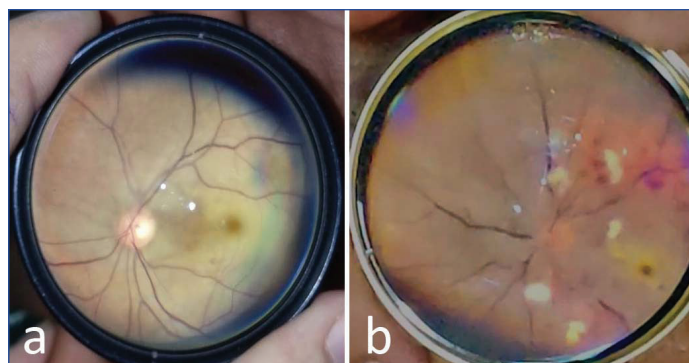


[Table/Fig-7]: a) Right eye complete ptosis with proptosis with complete ophthalmoplegia; b) Right eye smart phone fundus photography showing retinal edema with cherry red spot suggestive of CRAO.

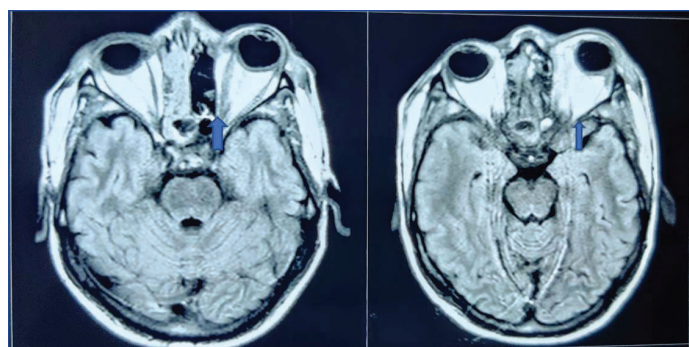
Out of 60 patients, most common retinal finding was central retinal artery occlusion in 35 patients [Table/Fig-8a] due to direct infiltration of central retinal artery by angioinvasion followed by combined retinal vascular occlusion [Table/Fig-8b] in five patients, disc pallor in four patients, optic atrophy in three cases and pre-existing diabetic retinopathy in 13 patients.

Every patient of ROCM was thoroughly investigated and CE-MRI brain with orbit with PNS was done to see the extent of disease and plan further management [Table/Fig-9,10]. Every case was followed-up for a period of three months and were managed in a multidisciplinary way accordingly.

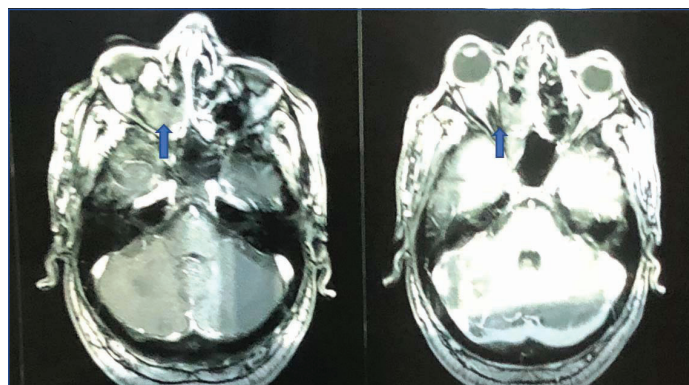
Other investigations were also done for confirmation of diagnosis, like Potassium Hydroxide (KOH) mount, culture and histopathological examination was done [Table/Fig-11 a-c].



[Table/Fig-8]: a) Left eye smart phone fundus photo showing CRAO with spared cilioretinal artery; b) Left eye smart phone fundus photo showing combined vascular occlusion.



[Table/Fig-9]: CE-MRI showing left eye proptosis with bulky muscles with intraconal and extraconal fat stranding with orbital apex involvement.



[Table/Fig-10]: CE-MRI showing mucosal thickening with soft tissue in right ethmoidal air cells, maxillary sinus and sphenoid sinus with blocked osteomeatal unit with right eye proptosis with enhancement of right perioptic CSF sheath.



[Table/Fig-11]: a) KOH mount (20X) showing broad aseptate hyphae s/o Mucormycosis; b) Culture tube showing creamy white growth at base which gradually darkens s/o Mucormycosis; c) Histopathological examination showing broad based, filamentous, aseptate and irregular hyphae s/o mucormycosis (H&E,40X).

DISCUSSION

The ROCM is an opportunistic angioinvasive infection caused by a group of saprophytic fungi, including *Rhizopus*, *Mucor* and *Absidia* [7]. Due to lack of population based studies and its relatively rare occurrence, exact incidence of ROCM in India is not known. However, in global data, estimated prevalence of mucormycosis is 70 times higher in India [3]. In post COVID-19 era, there was a sudden surge in cases of ROCM leading to significant morbidity and mortality in India. ROCM is classified into three categories: Possible, probable and proven ROCM. Mucormycosis is categorised as possible ROCM if

symptoms and signs of ROCM with concurrent or recent (<6 weeks) COVID-19 infection are present. When clinical symptoms and signs of ROCM are supported by diagnostic nasal endoscopy or radiologically by CE-MRI or Computed Tomography (CT) scan, it is classified as probable ROCM. If clinicoradiological features along with microbiological confirmation on direct microscopy or culture or histopathology with special stains or molecular diagnostics are present, it is classified as proven ROCM [11].

The CE-MRI brain with orbit is an important tool in diagnosing and monitoring progression of ROCM. It can definitely document orbital inflammation, muscle involvement, optic nerve involvement, optic sheath involvement, orbital apex involvement, cavernous sinus involvement and intracranial extension. But CE-MRI cannot document CRAO, CRVO, combined vascular occlusion, disc pallor, diabetic retinopathy and optic atrophy [12].

So, authors would strongly emphasise on fundus examination of every ROCM patient as it not only helps in categorising ROCM but also tell about the visual potential of affected eye. If CRAO is present on fundus examination, it will be stage 3c. Despite the availability of fundus camera in our institute, authors had to rely on smartphone fundus photography because of sick, immobile patients and it is an easy technique with short learning curve, not only for diagnosing and documenting fundus findings but also for monitoring its progression.

Smartphone Fundus Photography: Role in ROCM

Smartphone fundus photography is a fantastic and easily available tool for fundus examination with a short learning curve. As ROCM patients are sick, immobile patients and transportation is very cumbersome and not feasible, smart phone fundus photography is a better alternative. It is an amazing technique, not only for diagnosing and documenting fundus findings but also monitoring its progression. Most patients of ROCM are having complete ophthalmoplegia and its not feasible for them to focus target on fundus photograph machine, so smartphone fundus photography gives an extra edge to document the fundus finding by moving in different directions and focusing different quadrants [13].

Early diagnosis and management of ROCM is utmost important to reduce morbidity and mortality associated with this lethal disease, therefore a high index of suspicion in appropriate clinical setting is prerequisite. As this fungal infection is well known to cause bony erosions and necrosis in advanced stages, therefore CT scan has an extra edge over MRI. However, CE-MRI brain with orbit with PNS is more helpful in diagnosing early vascular invasion, intracranial spread and early perineural spread. Therefore, ideal investigation of choice for ROCM for monitoring its progression is a T2 weighted MRI with fat saturation sequences or Short-T1 Inversion Recovery (STIR) images [14].

For definite diagnosis of ROCM, microbiological confirmation on direct microscopy or culture or histopathology with special stains or molecular diagnostics is essential. On direct microscopy, characteristic ribbon-shaped, aseptate and irregularly branching hyphae are visualised in the tissue specimens and these findings are further strengthened if thrombosis of vessels signifying angioinvasion are seen. Even if culture report is negative and there is strong suspicion of ROCM, molecular diagnostic technologies like Polymerase Chain Reactions (PCR) can help in identification of the fungal species in histologic specimens [15].

The ROCM management is a medical as well as surgical emergency due to its aggressive angioinvasion nature. If ROCM is suspected based on risk factors, clinical features, and/or radiologic findings, early antifungal administration and extensive surgical debridement should be carried out empirically for better prognosis and outcome. The drug of choice for ROCM is intravenous (i.v.) liposomal amphotericin B in the dose of 5-10 mg per Kg body weight per day. If intracranial spread is present on MRI, high dose i.v. amphotericin B is given at 10 mg/kg body weight. Amphotericin is also used for local

instillation or irrigation of debrided cavities in surgical management. Transcutaneous Amphotericin B (TRAMB) is used as an adjuvant therapy in cases of progressive ROCM with significant thrombosis, done under aseptic conditions. The preferred site for TRAMB is above outer 1/3rd of inferior orbital rim. The complications which can be seen after TRAMB are chemosis, subconjunctival haemorrhage, retrobulbar haemorrhage and raised IOP. Post injection Tb Diamox 2tab stat, e/d moxifloxacin 0.5% and e/d carboxymethyl cellulose are given. Based on the clinical improvement, 5-7 injections of TRAMB are given [15].

Liposomal amphotericin B is given for several weeks in loading dose and when clinical improvement is achieved, the amphotericin is usually stepped down to oral posaconazole or isavuconazole. In the step down therapy, followed regimen for oral posaconazole (delayed-release tablet) is 300 mg twice daily on the first day, followed by 300 mg once daily and for oral isavuconazole, 200 mg (2×100 mg capsules) thrice daily for two days, followed by 200 mg once daily. However, oral posaconazole suspensions are not advisable due to inadequate bioavailability and fatty meal requirement for better absorption [15,16].

Limitation(s)

Number of subjects in this study was small. Hence the results obtained and conclusion drawn cannot be generalised till a study is done in which sufficiently large number of subjects are studied.

CONCLUSION(S)

The ROCM is an emerging ophthalmic emergency and early diagnosis and timely management is the key for not only saving sight, but also for saving the life of patient. CE-MRI brain with orbit is an important radiological investigation in diagnosing and monitoring progression of ROCM, but it also has few shortcomings. It cannot document various retinal manifestations of ROCM like CRAO, CRVO, disc pallor and optic atrophy. So, fundus examination of every ROCM patient must be done by a trained ophthalmologist, as it not only helps in categorising ROCM but also tell about the visual potential of affected eye. Exenteration on urgent basis should be considered for patients with CRAO and combined vascular occlusion, so that intracranial spread can be prevented and patient's life can be saved.

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