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### RESEARCH ARTICLE

#### RETROSPECTIVE ANALYSIS OF FUNDUS CHANGES IN POST COVID RHINO ORBITAL CEREBRAL MUCORMYCOSIS - A CASE SERIES

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#### Abstract

**Aim:** To study the fundus changes in post COVID- Rhino-orbital-cerebral mucormycosis.

**Methods:** The study was done by collecting data from 30 cases of ROCM admitted in GGH, Kurnool. Detailed history was taken along with systemic, ENT, ophthalmic and neurological examination and all necessary investigations were done including contrast enhanced MRI. Treatment was started with systemic and retrobulbar amphotericin-B injections. Fundus pictures were taken.

**Results:** All of them had history of infection with covid-19 dated about 3-5 weeks back. Among them 18 had corticosteroid administration, 12 had oxygen with nasal prongs/mask, 2 had high flow/non-invasive ventilation. All of them were diabetics and 21 were hypertensives. Most of them had orbital/ facial pain & edema, headache, 24 patients had proptosis, 16 had ptosis, 20 had ocular movement restriction, 18 had loss of vision. In Contrast Enhanced MRI scan, 28 cases showed diffuse PNS involvement, 4 had medial orbital involvement, 8 had diffuse orbital involvement, 18 had involvement of orbital apex, 6 had CNS involvement. Fundus examination revealed optic atrophy in 15 cases, 5 had CRAO and 3 had CRVO, 8 had diabetic retinopathy, 4 had hypertensive retinopathy, others had no significant abnormality.

**Conclusion:** Mucormycosis is a rapidly progressive angioinvasive fungal infection which has been on rise in India with the 2<sup>nd</sup> wave of COVID-19. Early diagnosis and management are essential to halt the spread of infection and prevent diminution of vision and therefore, further improve the visual outcome and overall prognosis of the patient.

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#### Introduction:-

Rhino-orbital-cerebral-mucormycosis (ROCM) is an invasive fungal infection caused from a fungus of the order mucorales.<sup>[1]</sup> It can spread quickly in those who are immunologically and metabolically impaired, such as those who have recently developed COVID-19 or those who have uncontrolled diabetes.<sup>[2]</sup> Invasion of blood vessels by fungal hyphae, infarction, and necrosis of host tissue are all features of this dreadful illness.<sup>[3]</sup> Early diagnosis and management of mucormycosis, triggered by a high index of clinical suspicion, are critical in determining the outcome.<sup>[3]</sup>

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The patient may present with symptoms of naso-sinusoidal involvement or orbital involvement depending on the stage of progression or spread of infection. The most common presenting symptoms are nasal stuffiness, nasal discharge, foul smell, eyelid/ peri-ocular/ facial edema &/or discolouration, facial pain, regional pain- orbit, paranasal, dental pain, proptosis, sudden diminution of vision, sudden ptosis, ocular motility restriction, diplopia, facial palsy, fever, altered sensorium, paralysis, worsening headache, focal seizures.<sup>[4]</sup>

The diagnostic investigations in ROCM are diagnostic nasal endoscopy, contrast enhanced MRI/ CT scan, microbiological confirmation by direct microscopy/ culture, histopathology with special stains ,and molecular diagnostics.<sup>[4]</sup>

Ocular fundus examination helps to know the causes for persistent diminution of vision in ROCM and the reasons for failure of improvement in vision even after administration of retrobulbar amphotericin-B injection in doses enough to control the infection. It may reveal thrombosis of central retinal artery or vein/ optic atrophy/ panophthalmitis.<sup>[5]</sup>

In this paper we presented 30 cases of ROCM , with emphasis on the fundus changes.

### **Methods:-**

Data was collected from 30 cases of ROCM admitted and treated in GGH, Kurnool in July 2021.

The patients were in the age group of 50-75years, among them 16 were male and 14 were female.

Evaluation at presentation included a detailed history taking, careful systemic, ENT, ophthalmic, neurological examination. All the necessary haematological, radiological, microbiological investigations were done to assess the general condition of the patient and to know the extent of the disease.

All of them had history of infection with COVID-19 dated about 3-5 weeks back. The diagnosis of COVID-19 was based on RTPCR test on nasopharyngeal/oropharyngeal swabs. Among them, 2 were asymptomatic, 4 had home care, 24 were hospitalised, 18 had corticosteroid administration, 14 had remdesivir, 12 had oxygen with nasal prongs/mask, 2 had high flow/non-invasive ventilation. All patients were diabetics with uncontrolled blood sugars and 21 were hypertensives.

Most of them had orbital/facial pain & edema and headache, 24 patients had proptosis, 16 had ptosis, 20 had ocular movement restriction, 18 had loss of vision.

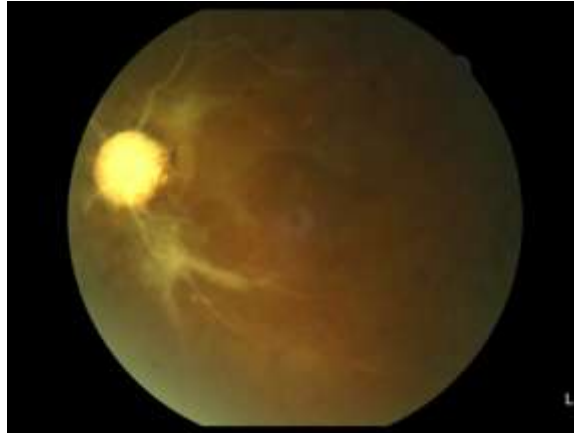
The diagnosis of mucormycosis was made by histopathologic, cytopathologic or direct microscopic examination of the biopsy specimen, or the deep or endoscopy- guided nasal swab showing fungal hyphae or from a positive culture report.

Contrast enhanced MRI scan revealed rhino-orbital-cerebral involvement in every patient. 28 cases showed diffuse PNS involvement, 4 had medial orbital involvement, 8 had diffuse orbital involvement, 18 had involvement of orbital apex, 6 had CNS involvement.

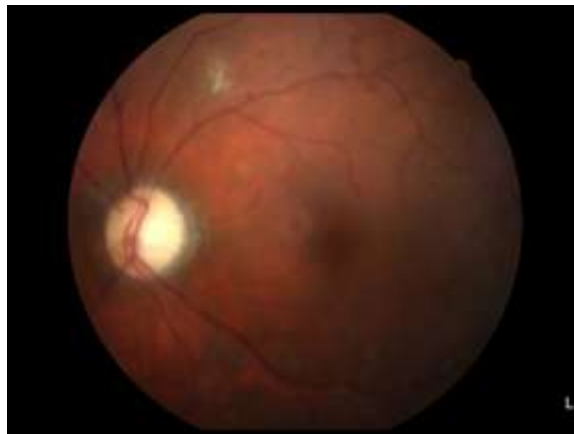
Treatment with systemic liposomal amphotericin-B was started as soon as the diagnosis of mucormycosis was established with monitoring of renal parameters. Retrobulbar amphotericin-B injections were given in cases with orbital involvement. Retrobulbar amphotericin-B injections were given in a dose of 3.5 mg in 1ml on alternate days. Treatment was also instituted to stabilize the underlying metabolic derangement. Careful monitoring of fasting blood sugar levels was done and treatment was instituted with the aim of achieving better glycemic control. FESS/ PNS debridement was done. Step down treatment was with oral posaconazole.

### **Results:-**

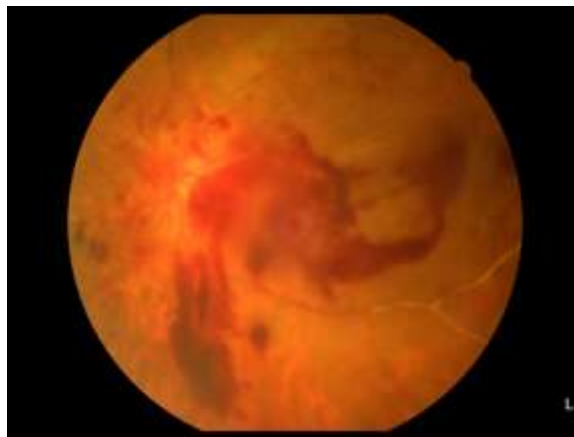
Fundus examination was done after completing the course of retrobulbar amphotericin-B injections in these patients. 15 cases showed optic atrophy (primary or secondary) , 5 cases showed CRAO and 3 cases showed CRVO, 8 cases had diabetic retinopathy changes, 4 cases had hypertensive retinopathy, others had no significant abnormality.



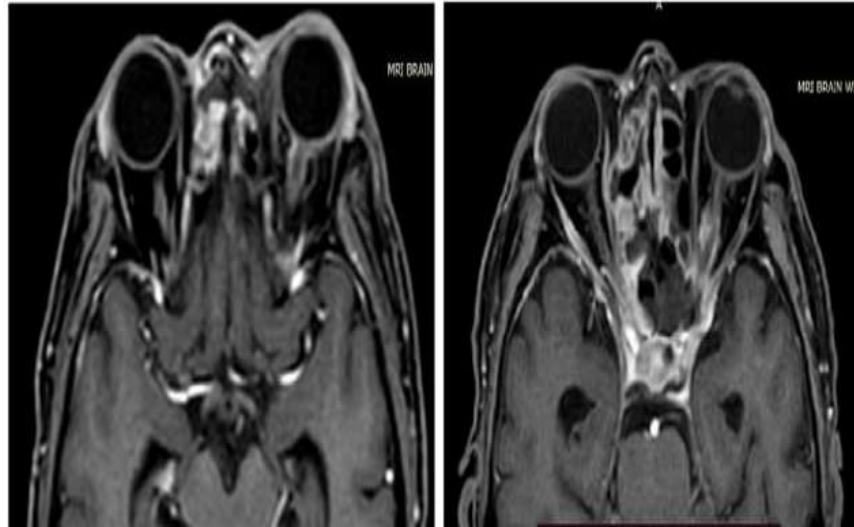
**Fig 1:-** Fundus image showing Optic atrophy with CRAO with presence of ghost vessels.



**Fig 2:-** Fundus image showing Optic atrophy with dot and blot haemorrhages in the supero-temporal quadrant.



**Fig 3:-** Fundus image showing extensive haemorrhages near the optic disc and occluded vessel in the infero-temporal quadrant.



**Fig 4:-** Image 1(left side):-This is a contrast enhanced-MRI showing thickening with heterogeneous enhancement of intraorbital part of left optic nerve suggestive of optic neuritis.

Image 2(right side):- This is a contrast enhanced MRI showing ill-defined heterogenous enhancing soft tissue in the left orbital apex and heterogenous enhancement of left optic nerve suggestive of optic neuritis.

### Discussion:-

Mucormycosis is caused by filamentous fungi in the mucoraceae family of the order mucorales. They are common and can be found in soil and decaying organic waste. Mucormycosis, which was previously classed as a rare fungal illness, has been reclassified as an emerging pathogen. Mucormycosis is most common in people with diabetes mellitus, particularly diabetic ketoacidosis, as well as immunosuppressive states such as steroid therapy, hematologic malignancies, and organ transplant recipients.<sup>[6]</sup> ROCM commonly begins with inhalation of fungal spores (sporangiospore), which is followed by invasion of the nasal mucosa and the development of coenocytic hyphae that can spread.<sup>[7]</sup> Angioinvasion is a characteristic of Mucormycosis that is one of the key mechanisms of spread and a cause of tissue necrosis.<sup>[8]</sup> In normal healthy people, macrophages prevent infection by phagocytosis and oxidative killing of spores, but in those who are immunocompromised, spores evade the oxidative metabolites and defensins which are secreted by the macrophages and reach the endothelium lining. The penetration of endothelial cells is a crucial step in angioinvasion, and the receptor implicated in the process is glucose-regulator protein GRP78. Due to high amounts of glucose, free iron, and ketone bodies, the tissue microenvironment in diabetes patients is altered, inducing stress on the endoplasmic reticulum, which leads to upregulation of GRP78 receptors. Spores produce the ligand cot H, which binds to GRP78 receptors on the nasal endothelium, allowing them to enter the blood vessel. Angioinvasion is caused by spores and hyphae interacting with EDGF on endothelial cells.<sup>[6]</sup> The hyphae grow in the sinuses at first, then spread mostly through direct tissue invasion.<sup>[7]</sup> Orbital invasion is most usually caused by the lamina papyracea, NLD, ethmoid foramina, and vascular channels perforating the medial orbital wall. It can spread by destroying the bony orbital wall from the maxillary sinus in rare cases of aggressive illness.<sup>[2]</sup> The fungus breaches the blood vessel wall, causing mechanical and toxic damage to the intima, resulting in thrombosis, and then spreads to the lymphatics and veins. These thrombosis cause tissue necrosis by causing emboli and vascular occlusion.<sup>[6]</sup> Soft tissue infiltration and edema of retroorbital fat around the extra ocular muscles are the signs of early orbital infection. Proptosis is caused by a diffuse orbital infection. When both the optic canal and the superior orbital fissure are affected, the orbital apex is said to be involved.<sup>[2]</sup> Visual impairment (CN II involvement), ophthalmoplegia with mydriasis and ptosis (CN III, IV, VI involvement), RAPD, periorbital/facial pain, and hypoesthesia of the forehead (CN V involvement) are all symptoms of orbital apex involvement. Ocular invasion is uncommon, however it can occur as a result of either direct or hematogenous spread. Direct spread of fungal infection causes thickening and enhancement of the ocular coats. Choroiditis is occurs by the infection spreading via the bloodstream and creating focal infective deposits in the choroid. Under microscopic examination, the choroiditis consists of granulomatous inflammation with pathogenic organisms in the core and suppurative or inflammatory cells surrounding it. Retinitis is caused by the further local spread of the fungal hyphae into the retina. Vitritis develops when the infection spreads from the retina to the vitreous, resulting in

endophthalmitis.<sup>[9]</sup> Direct optic nerve infection by mucormycosis / occlusion of blood supply optic nerve, CRAO, ophthalmic artery occlusion, CRVO, and fungal endophthalmitis are all causes of visual impairment in ROCM.<sup>[10]</sup> Isolated optic nerve involvement means that the infection has spread through branches of the ophthalmic artery, signalling the need for aggressive treatment.<sup>[2]</sup> Through the superior orbital fissure, the infection can extend to the cavernous sinus. It can further spread to the central nervous system via the orbital apex, cribriform plate, cavernous sinus, or blood vessels. In rare cases, the infection might spread to the contralateral orbit or eyeball.<sup>[8]</sup>

Early and aggressive management helps to stop the further spread of infection and improves prognosis. Mucormycosis can be successfully treated in four steps: (1) early diagnosis of the disease; (2) reversal of underlying predisposing risk factors, if possible; (3) surgical debridement where ever necessary; and (4) prompt antifungal therapy. Awareness of warning symptoms and signs, as well as a high index of clinical suspicion, are necessary for an early diagnosis of mucormycosis, which can be confirmed by microbiological and radiological testing. When treating mucormycosis patients, it is vital to address the underlying metabolic abnormalities and the impairments in host defence. If possible, immunosuppressive medications, particularly corticosteroids, should be used at lower doses or stopped altogether. In diabetic ketoacidosis, aggressive treatment to quickly restore euglycemia and normal acid-base status is crucial. Early treatment with intravenous liposomal amphotericin-B, as well as surgical debridement of the affected tissues, are essential for better outcomes. The infected tissues are avascular, necrotic and lead to poor penetration of antifungals to the site of infection. It represents an unsalvageable nidus of fungal elements. As a result, the total elimination of mucormycosis necessitates debridement of the necrotic tissues. Once bleeding tissue is seen at the margins, the debridement is stopped.<sup>[11]</sup> In case of orbital involvement, retrobulbar amphotericin-B injections are given with the hope of preserving useful vision. Advanced cases of ROCM necessitates potentially mutilating surgical procedures such as maxillectomy, palatal resection, and orbital exenteration.<sup>[2]</sup>

### Conclusion:-

Mucormycosis is a potentially fatal, rapidly progressive angioinvasive fungal infection in which the visual outcome and overall prognosis of the patient depends on early diagnosis and prompt management. The vision can be affected by direct invasion of optic nerve by the fungus or ischemia of the optic nerve, involvement of major blood vessels like ophthalmic artery, central retinal artery and central retinal vein compromising the blood supply of retina. Fundus examination of these patients thus reveals optic atrophy/ CRAO/ CRVO as the cause for visual impairment and changes of diabetic retinopathy/ hypertensive retinopathy as a clue to the underlying risk factors and/or comorbidities.

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