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NON- AXIAL PROPTOSIS ASSOCIATED WITH COMPRESSIVE OPTIC NEUROPATHY AND RETINAL VENOUS OCCLUSION SECONDARY TO SINO-ORBITAL MUCORMYCOSIS-A MULTIDISCIPLINARY MANAGEMENT

[1]Dr. Md.Ruksana, [2]Dr.B.Dharma Raju, [3]Dr. Leshna Kopparapu, [4]Dr.I.Mounika, [5]Dr.Y.Roja.

[1]Junior Resident: Department of Ophthalmology: NRI Institute Of Medical Sciences, Visakhapatnam, Andhra Pradesh, India.

[2]Professor: Department of Ophthalmology: NRI Institute Of Medical Sciences, Visakhapatnam, Andhra Pradesh, India.

[3]Junior Resident: Department of Ophthalmology: NRI Institute Of Medical Sciences, Visakhapatnam, Andhra Pradesh, India.

[4]Junior Resident: Department of Ophthalmology: NRI Institute Of Medical Sciences, Visakhapatnam, Andhra Pradesh, India.

[5]Junior Resident: Department of Ophthalmology: NRI Institute Of Medical Sciences, Visakhapatnam, Andhra Pradesh, India.

***Corresponding author**

Dr. **Md.Ruksana,,**

Junior Resident, Department of Ophthalmology, NRI Institute Of Medical Sciences, Visakhapatnam

Email : ruksanamohammad2741@gmail.com.

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ABSTRACT

Introduction: Sino-orbital-cerebral-mucormycosis, previously referred to as orbital zygomycosis , refers to the presentation of pathologic symptoms in the orbit as a result of fungal infections caused by fungi in the order Mucorales, most commonly by the species Rhizopus oryzae. Mucormycosis usually occurs in an immunocompromised host and presents with initial symptoms such as vision loss, ptosis, diplopia and external ophthalmoplegia. Left untreated, sino-orbital-mucormycosis can progress to acute vision loss, metastasis (brain, sinuses) and death.

Case presentation: The current case came with complaint of defective vision RE, protrusion of eyeball and drooping of right upper lid since 1 month. Defective vision RE-insidious in onset gradually progressive since 1 month. Forward protrusion of RE insidious in onset gradually progressive since 1 month, H/o right side facial pain which is sharp ,severe, radiating to right temperoparietal region associated with facial heaviness on bending forward and associated with swelling below right eye – insidious & gradually progressive. Drooping of right upper eye lid insidious in onset, gradually progressive since 20 days. Past history recovery from covid infection present. Diagnosed as Non –axial proptosis associated with compressive optic neuropathy and retinal venous occlusion secondary to Sino-orbital mucormycosis. **Conclusion**: A rare but fatal fungal infection is ought to be kept in mind nowadays. This case highlights the importance of early diagnosis, management and evaluation for good prognosis, decreasing the morbidity.

Keywords: fungal infection, sinusitis, Histopathological examination, Magnetic resonance imaging, Mucormycosis

INTRODUCTION:

Mucormycosis is the most fulminant form of Zygormycosis caused by Mucorales species of the phylum Zygomycota described as a potentially lethal infection occurring mostly in immunocompromised hosts, particularly in those with diabetes mellitus, leukaemia and lymphoma. The incidence rate of mucormycosis globally varies from 0.005 to 1.7 per million population. In Indian population its prevalence is 0.14 per 1000. Globally the fatality rate of mucormycosis is 46%. [1,2] The most common risk factors being DM, immunosuppressive therapy, leukaemias, neutropenias. Fungal spores are inhaled causing sinusitis which eventually spreads to adjacent structures such as the orbit and cavernous sinuses with extension to intracranial vasculature and brain.[3] An extremely rarely reported complication of sino-cerebral-mucormycosis is optic nerve infarction.

CASE HISTORY

A 58-year female who is housewife with complaint of defective vision RE, protrusion of eyeball and drooping of right upper lid since 1 month. Defective vision RE- insidious in onset gradually progressive since 1 month. Forward protrusion of RE insidious in onset gradually progressive since 1 month, H/o right side facial pain which is sharp ,severe, radiating to right temperoparietal region associated with facial heaviness on bending forward and associated with swelling below right eye – insidious & gradually progressive. Drooping of right upper eye lid insidious in onset, gradually progressive since 20 days. With no h/o double vision or swelling of lids, watering, no h/o difficulty in swallowing or change in voice, no h/o trauma, no h/o tremors, palpitations or neck swelling, no h/o photophobia, and no h/o radio/chemotherapy . She is known hypertensive since 3years and diabetic since 1 month. Underwent RE cataract surgery 1year ago. History of recurrent bilateral nasal blockage present. No h/o pulmonary TB, Epilepsy, bronchial asthma,CVA . On general Examination patient is conscious, coherent and well oriented in time, place and person, Moderately built and nourished, No Pallor, icterus, cyanosis, clubbing, pedal edema or lymphadenopathy, no palpable lymph nodes, preauricular ,submandibular , cervical lymph node, no evidence of skin changes or dryness, no evidence of tremors and no evidence of thyroid acropachy. Stable vitals and no significant finding in other systems . On nasal examination Right nasal cavity- inferior turbinate hypertrophy ,congested nasal mucosa and mucopurulent blackish debris present with fungal elements extending to middle meatus and nasopharynx

Left nasal cavity – grade 1 adenoid hypertrophy , spur+ , Bilateral frontal, ethmoidal, maxillary sinus tenderness present. Head posture normal, face asymmetrical, ocular alignment is not maintained, ocular movements- All movements restricted in all gazes in right eye. All movements are full free and painless in left eye.

Table-1: Ocular examination

	RE	LE
UCVA	6/60	6/24
BCVA	6/24	6/18
NV	N12	N12

CV	uncooperative	uncooperative
IOP	13mmhg	12mmhg
LIDS AND ADNEXA	UL Mechanical ptosis, Fullness +superior, medial orbital space and maxillary space	UL retraction(Herring's law)
LACRIMAL APPARATUS	WNL	WNL
CONJUNCTIVA	Mild Conjunctival congestion +	normal
LIMBUS	normal	normal
SCLERA	normal	normal
CORNEA	clear	clear
ANTERIOR CHAMBER	Normal depth	Normal depth
IRIS	NCNP	NCNP
PUPIL	RAPD -1	NSRL
LENS	Pseudophakia	NS 1 with PSCC

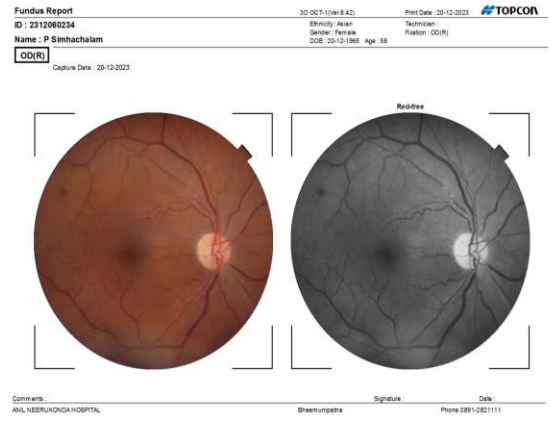
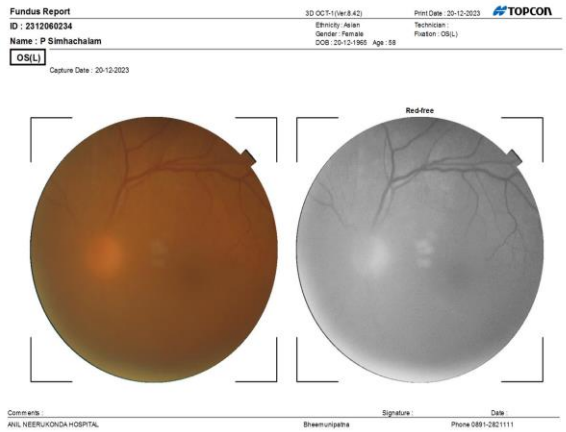
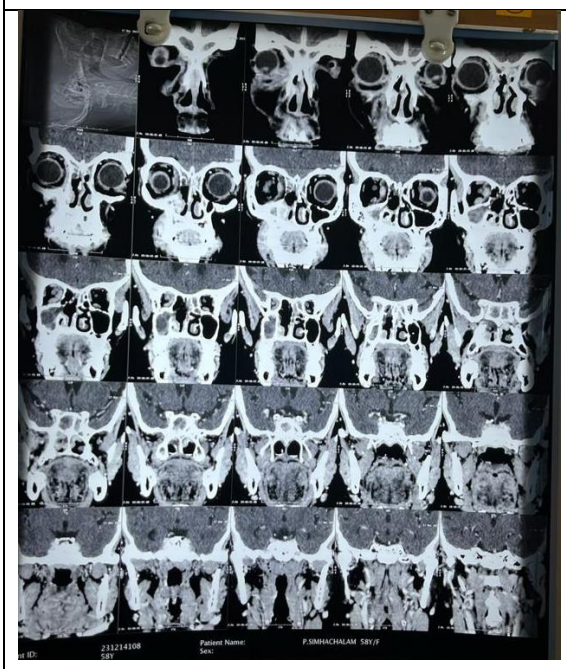
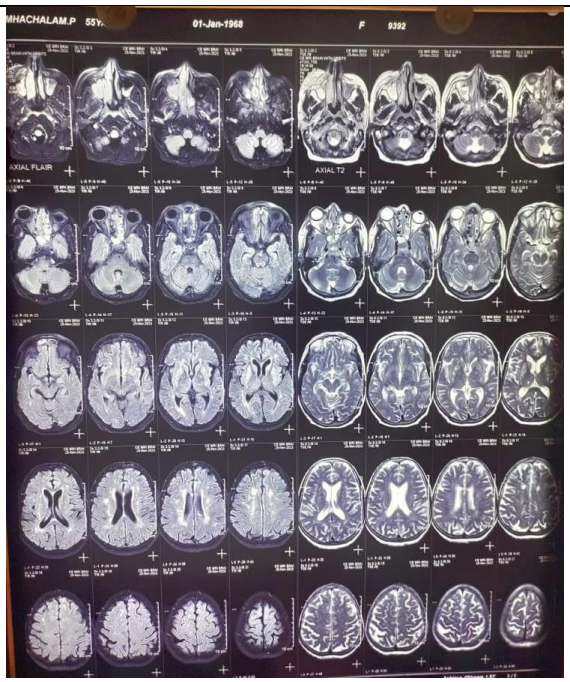
Table-2: Ptosis Measurement

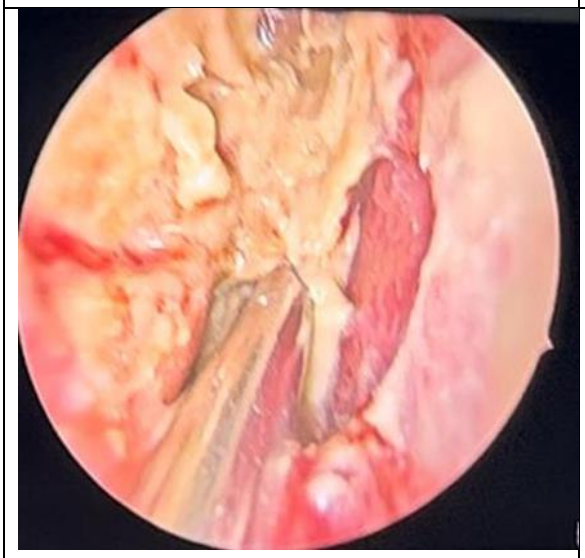
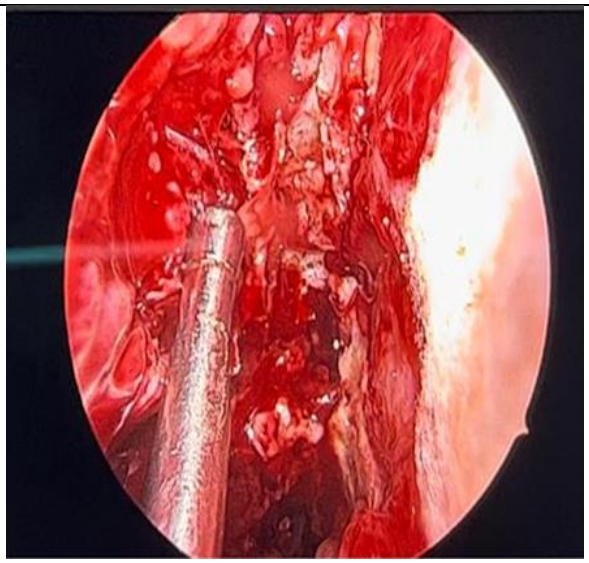
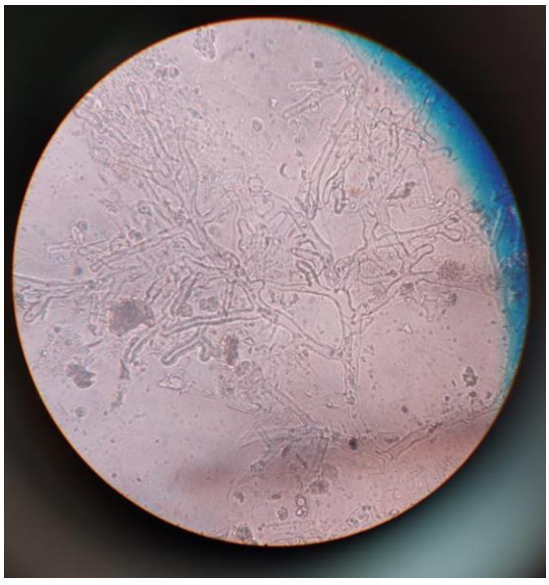
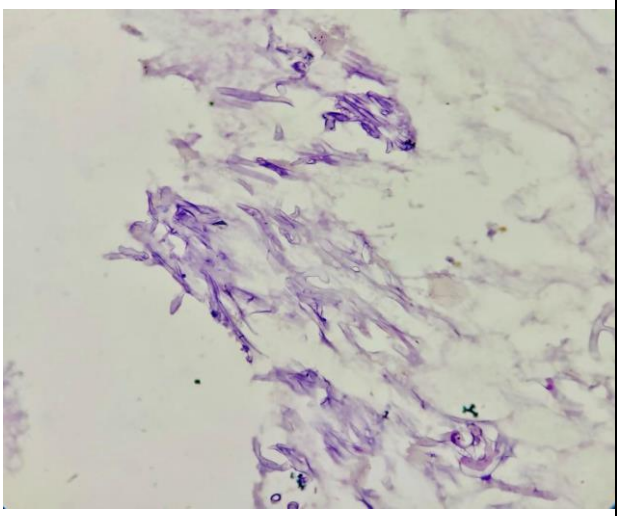
	RE	LE
MRD1	2mm	6mm
MRD2	5mm	5mm
PFH	7mm	11mm

Table-3 : Fundus Examination

	RIGHT EYE	LEFT EYE
MEDIA	Pseudophakia	Lenticular opacities with coarse vitreous floaters
OPTIC DISC	Diffuse pallor with clear cut margins	normal
C:D RATIO	0.2:1	0.2:1
BLOOD VESSELS	Arteriovenous narrowing + Av crossing changes+	Arteriovenous narrowing+
FR	+	+
PERIPHERAL RETINA	Normal	Normal

Table-4: Exophthalmometry: RE- 25mm , LE- 20mm
Forward displacement of RE- 5mm
Horizontal dystopia of RE - 3mm
Vertical dystopia of RE- 4mm upwards

FUNDUS- RE OPTIC DISC- DIFFUSE PALLOR	**FUNDUS-LE** FNMC
	
CT SCAN PNS	**MRI BRAIN WITH ORBITS**
	
CT SCAN PNS : Heterogeneously enhancing mucosal thickening noted involving bilateral frontal, ethmoidal, sphenoid and right maxillary sinuses. Adjacent facial bones appear relatively lucent with ill-defined erosions within.	MRI BRAIN WITH ORBITS: Heterogenous complete mucosal thickening noted involving the right maxillary sinus, right ethmoidal, right frontal, right sphenoidal sinus noted with rarefaction, irregularity in the floor and the medial wall of right orbit with extension of hyperintense lesions or infiltration involving the right retroorbital region, right medial rectus, inferior rectus, superior rectus and oblique muscles noted there is also associated right sided proptosis with periorbital edema noted in post contrast

	heterogenous enhancement of mucosal thickening and retroorbital regions noted possibility of infiltrative fungal sinusitis .
FESS PROCEDURE-	
	
TISSUE FOR KOH:  TISSUE FOR KOH: Plenty of broad ribbon like septate hyphae suggestive of mucormycosis	**HPE REPORT**:  Histopathological Examination Report: Photomicrograph shows collection of broad aseptate fungal hyphae, Mucormycosis (PAS stain 40x)

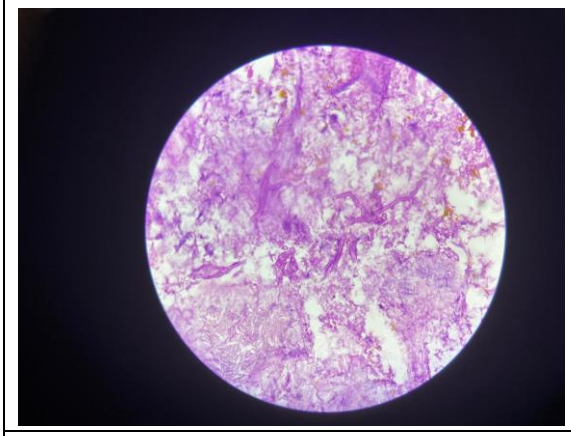
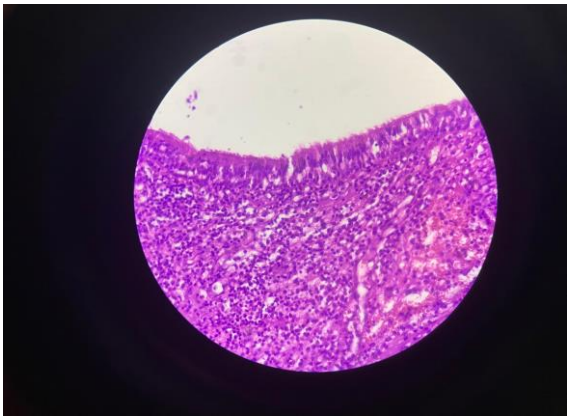
HPE	**HPE**
	
HPE REPORT: Photomicrograph shows colony of thick broad aseptate hyphae with irregular branching, Mucormycosis(H and E 40x)	**HPE REPORT**: Photomicrograph shows ciliated columnar epithelium showing chronic inflammatory cell infiltrate predominantly lymphocytes (H and E 10X)

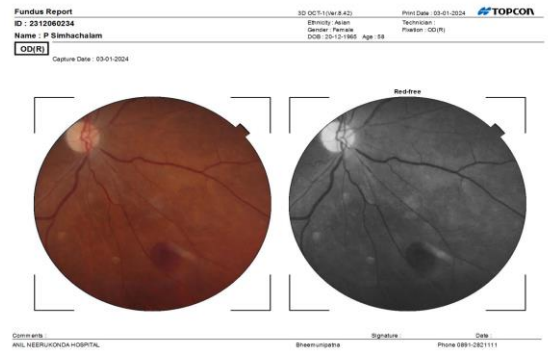
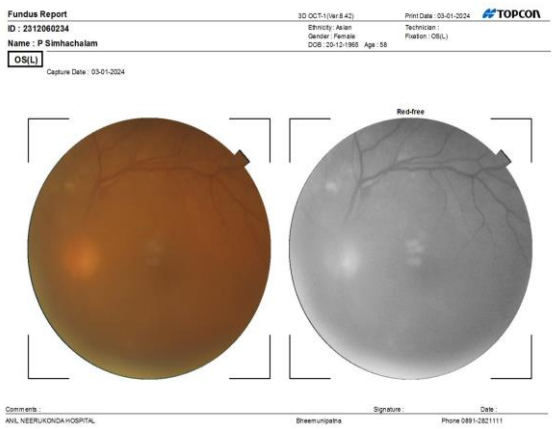
Table-5: Exophthalmometry readings post orbital debulking surgery

Forward displacement of RE	1mm
Horizontal dystopia of RE	2mm
Vertical dystopia of RE	1mm

Post surgery VA : - RE CF 1mt ph NI , LE – 4/60 ph 6/24

Table-6: Post Surgery Fundus Examination

	Right Eye	**Left Eye**
MEDIA	Pseudophakia	Lenticular opacities with coarse vitreous floaters
OPTIC DISC	Atrophic cupping	normal
C:D RATIO	0.2:1	0.2:1
BLOOD VESSELS	Arteriolar narrowing Calcific plaques + superotemporal in both arteries and veins	normal
FR	+	+
PERIPHERAL RETINA	Localized haemorrhage + inferonasal quadrant	normal

Post op RE fundus : Optic atrophy with inferonasal BRVO 	**Post op LE fundus**: FNMC 
	
Before surgery	After surgery

Diagnosis:
RE-Non –axial proptosis associated with compressive optic neuropathy and retinal venous occlusion secondary to Sino-orbital mucormycosis.

DISCUSSION:

Mucormycosis is an uncommon entity but upsurge of cases were noted in the cohort of post covid immunocompromised patient population, in the backdrop of humid and tropical climate of central Asian countries like India. Mucormycosis is rare opportunistic fungal infection characterized by infarction and necrosis of host tissues that results from invasion of the vasculature by hyphae. 70% of sino-orbital-cerebral mucormycosis cases have been found to be in patients with diabetes mellitus. In high risk individuals, this diagnosis should be suspected if there is unilateral facial pain or swelling, orbital swelling or proptosis. Diagnosis is

classically dependent on clinical features, pathological findings and imaging plays an important role in defining the extent of involvement.

Mucormycosis, depending on organ/s involved, is further sub classified as, Sino-orbital-cerebral mucormycosis which is most commonly observed, followed by cutaneous, pulmonary, disseminated, renal and gastrointestinal [4]. The burden in India is specifically high owing to high prevalence of diabetes mellitus in our population which is a major risk factor to sinocerebral forms of mucormycosis. and hence, is estimated to be 70 times higher in Indian population [5]. The fungus, being highly angioinvasive, tends to spread rapidly from its initial lodgement site of nasal cavity to maxillary and ethmoid sinuses, thereafter sequentially to orbits, sphenoids, cavernous sinus, base of skull, meninges and finally the cerebral cortex. Mucor species is known to cause perineural invasion, intraneural invasion and neural necrosis which contributes to its neuro-invasive and neuro-destructive properties.
The base of skull forms the first line of barrier to be breached in the transition to cerebral forms. The literature available on patterns of skull base involvement of covid associated mucormycosis is scarce and has consisted mostly of case reports.

In our study is a case of right eye Non –axial proptosis associated with compressive optic neuropathy and retinal venous occlusion secondary to Sino-orbital mucormycosis.
CT scan showed Heterogeneously enhancing mucosal thickening involving bilateral frontal, ethmoidal, sphenoid and right maxillary sinuses. Adjacent facial bones appear relatively lucent with ill-defined erosions within. MRI showed Heterogenous complete mucosal thickening noted involving the right maxillary sinus, right ethmoidal, right frontal, right sphenoidal sinus noted with rarefaction, irregularity in the floor and the medial wall of right orbit with extension of hyperintense lesions or infiltration involving the right retroorbital region, right medial rectus, inferior rectus, superior rectus and oblique muscles noted there is also associated right sided proptosis with periorbital edema noted in post contrast heterogenous enhancement of mucosal thickening and retroorbital regions noted possibility of infiltrative fungal sinusitis .

One of initial cases was reported by Mehta and Pandey in 2020 for an elderly diabetic male patient who had who developed orbital cellulitis few days after receiving systemic corticosteroids as a treatment modality for COVID-19 infection. MRI scan showed significant mucosal thickening in the ipsilateral paranasal sinus, preseptal and retrobulbar tissues. [6]. Another significant case was reported by Werthman-Ehrenreich in 2021 where a middle aged female developed mucormycosis with orbital compartmental syndrome following covid infection. CT scan of nose and paranasal sinuses showed mucosal thickening of the maxillary and ethmoidal sinuses and MRI brain showed ischemic infarctions and frontal lobe abscess with cerebral edema [7].

Mekonnen et al. reported a case of invasive fungal sinusitis in a Covid 19 patient with opacification of the unilateral paranasal sinuses, lamina papyracea dehiscence, right orbital proptosis, and cellulitis [8]. In a case series of six patients by Sen et al. one of the patient had concurrent Covid 19 and rhino-orbital mucormycosis. Majority had intracranial extension with meningitis, cerebritis, cavernous sinus thrombosis and internal carotid artery thrombosis [9].

As per literature in pre covid era, there was a retrospective study in 2004 by Bhansali A et al. where they identified 35 consecutive cases of Sino-orbito-cerebral mucormycosis. Ophthalmic and extensive cerebral involvement predominated the clinical picture [10]. There are two interesting case reports by Alsubhaiabani AH et al. in 2012 and Chen IE et al. in 2019 respectively, where pathological involvement and presentation were optic neuritis and optic atrophy which developed 2 weeks after being diagnosed with mucormycosis. Perineuritis and neuroinvasion by fungus was demonstrable as high signal intensity in contrast-enhanced MRI scans [11,12].

As per review of 929 reported cases of mucormycosis patients by Roden et al. [13], sinocerebral forms of mucormycosis was commonest in patients with diabetes mellitus and survival rates were highest for patients who were treated with dual modality of surgery and antifungal therapy as compared to those who treated with surgery or Amphotericin B alone.

In a landmark study by Chakravarty A et al. in 2013, initial site of pathology in intracranial involvement was cavernous sinus. This also rationalised the early symptoms of III, IV and VI cranial nerve involvement leading to diplopia, restricted extraocular movements in sino-orbital forms. This eventually also invaded the trigeminal nerve branches V1 and V2 that traverse through it [14]. The commonest imaging lesions noted in intracranial mucormycosis are cavernous sinus thrombosis, cerebral infarction and internal carotid artery occlusion [15]

Headache and proptosis/ptosis were the commonest symptoms followed by retroorbital pain, facial pain and paraesthesias [16]. Extraocular movement abnormalities were the commonest sign noted. The imaging modalities like CT scan and MRI have an immense role in mapping out the disease localization, spread to vital surrounding soft tissues, and detecting any bone erosion which helps in early diagnosis and surgical planning [17].

Amphotericin B injection is the gold standard antifungal agent for mucormycosis but it achieves suboptimal tissue concentrations as it crosses blood brain barrier [18]. For sino-orbital-cerebral form of mucor, efficacy of antifungal regimen is increased by combining liposomal Amphotericin B with an extended spectrum azole, either posaconazole or isavuconazole, may increase the likelihood of achieving effective drug concentrations in the brain. The cumulative drug dose required depends on multiple factors like zone of sinonasal involvement, extent of surgical debridement, immune status of the patient, renal parameters of the patient and impending cerebral spread. A recent systematic review by Cornely and colleagues provides dose recommendations for various stages of mucormycosis [19].

CONCLUSION:

Sinoorbital mucormycosis is an increasingly common infection especially in developing countries, and is a major threat to patients with poorly controlled diabetes mellitus. Ischemic involvement of optic nerves, retinal venous occlusions, although a rare complication, should be considered in cases presenting with visual symptoms. Sinoorbital mucormycosis is best

managed by a multidisplinary team. Immediate initiation of intravenous antifungals, reversing the patients immunocompromised state, and endoscopic surgical debridement are the basis of treatment.

This case highlights the importance of early diagnosis, management and evaluation for good prognosis, decreasing the morbidity.

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