• COVID-19 and Ophthalmology •

Clinical outcome of orbital apex syndrome in COVID associated mucormycosis patients in a tertiary care hospital

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Abstract

● **AIM:** To share clinical pattern of presentation, the modalities of surgical intervention and the one month post-surgical outcome of rhino-orbito-mucormycosis (ROCM) cases.

● **METHODS:** All COVID associated mucormycosis (CAM) patients underwent comprehensive multidisciplinary examination by ophthalmologist, otorhinolaryngologist and physician. Patients with clinical and radiological evidence of orbital apex involvement were included in the study. Appropriate medical and surgical intervention were done to each patient. Patients were followed up one-month post intervention.

● **RESULTS:** Out of 89 CAM patients, 31 (34.8%) had orbital apex syndrome. Sixty-six (74.2%) of such patients had pre-existing diabetes mellitus, 18 (58%) patients had prior documented use of steroid use, and 55 (61.8%) had no light perception (LP) presenting vision. Blepharoptosis, proptosis, complete ophthalmoplegia were common clinical findings. Seventeen (19.1%) of such patients had variable amount of cavernous sinus involvement. Endoscopic debridement of paranasal sinuses and orbit with or without eyelid sparing limited orbital exenteration was done in most cases, 34 (38.2%) patients could retain vision in the affected eye.

● **CONCLUSION:** Orbital apex involvement in CAM patients occur very fast. It not only leads to loss of vision but also sacrifice of the eyeball, orbital contents and eyelids. Early diagnosis and prompt intervention can preserve life, vision and spare mutilating surgeries.

● **KEYWORDS:** rhino-orbito-cerebral mucormycosis; COVID associated mucormycosis; orbital exenteration; endoscopic paranasal sinus debridement; orbital apex syndrome

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INTRODUCTION

The ongoing pandemic of COVID-19 disease caused by severe acute respiratory syndrome corona virus 2 (SARS-CoV-2) has prompted wide spread use of steroids as a life saving measure. This wide spread use of steroids coupled with pre-existing as well as post COVID diabetes mellitus has led to huge surge of mucormycosis cases involving sinuses, orbit and brain. A combination of pre-existing diabetes mellitus and therapeutic use of steroids for SARS-CoV-2 infection may have acted synergistically leading to this sudden surge of rhino-orbito-cerebral mucormycosis (ROCM) cases. Prior to the COVID-19 pandemic mucormycosis was usually seen among patients with immunocompromised status like organ transplant recipient and uncontrolled hyperglycemia. The prevalence of such cases was low[1].

Filamentous fungi of family mucoraceae is the causative agent for this devastating opportunist infection. Immunocompetent individuals are rarely affected. SARS-CoV-2 infection causes severe weakening in both innate and humoral immune system. Additionally, the widespread use of steroids has resulted in poorly controlled hyperglycemia. The resultant acidic

environment has led to favorable condition for fungal invasion and proliferation[2-3].

In ROCM, the fungal invasion occurs through the nasal mucosa into the paranasal sinuses like maxillary and ethmoid sinus. From the sinuses it enters into the orbit mostly by eroding the medial orbital wall. Once into the orbit, it rapidly involves the orbital apex leading to complete ophthalmoplegia, ptosis and loss of vision. From the orbital apex, it ultimately reaches brain causing ischemic necrosis of brain parenchyma leading to severe debilitation and death. The natural history of the disease progression is very rapid and requires early and prompt intervention[3].

ROCM cases presenting as orbital apex syndrome requires urgent surgical intervention which may range from endoscopic orbital debridement to exenteration along with endoscopic or open debridement of necrotic tissue from nasal cavity and paranasal sinuses. The surgical intervention may be quite exhausting and mutilating at times when delayed. Local and systemic use of broad-spectrum antifungals like amphotericin B and posaconazole acts synergistically in the peri-operative period[4].

In this prospective observational analysis regarding the prevalence and treatment outcome of ROCM patients presenting with orbital apex syndrome, the authors intend to share clinical pattern of presentation, the modalities of surgical intervention and the one-month post-surgical outcome of such cases.

SUBJECTS AND METHODS

Ethical Approval This study was approved by the IPGME&R Research Oversight Committee and adhered to the tenets of the Declaration of Helsinki. Informed consent was obtained from all subjects.

This study has been conducted in a tertiary referral center designated to treat COVID associated mucormycosis (CAM) patients with state-of-the-art multidisciplinary facility. Among 89 patients who presented with CAM in our center clinical features suggestive of orbital apex syndrome was found in only 31 patients (34.8%) between May 2021 to July 2021 (Figure 1). These 31 patients had undergone comprehensive ophthalmological, otorhinolaryngological and systemic examinations. Neuro-orbito and facial imaging in the form of contrast magnetic resonance imaging (MRI) and computerized tomography (CT) scan was done in each case to confirm disease localization and extent of tissue damage. A multi-disciplinary team involving faculties from ophthalmology, otorhinolaryngology, neurology, endocrinology and internal medicine jointly evaluated each case. Appropriate surgical intervention for each case was unanimously planned and executed after taking written informed consent from patient or his/her near relatives. Appropriate peri-operative anti-fungal systemic coverage was ensured. Injection amphotericin B was given for 4-6wk as 1 mg/kg body weight followed by tablet posaconazole 300 mg/d for 90d. Each patient was followed up for 1mo. Weekly microbiological surveillance of the scrapings from the orbit and sinuses were done to detect recurrence. The clinical outcome of each patient was documented at one-month post operatively. Data was analyzed using standard statistical software and multiple regression analysis has been performed to assess the possible risk factors.

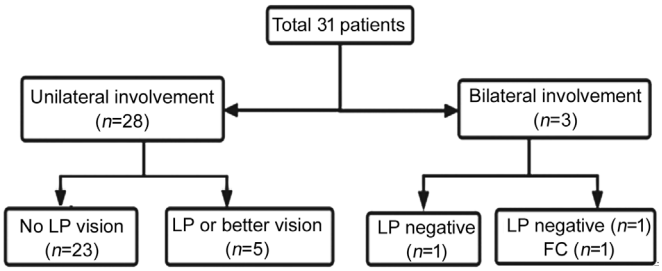

Figure 1 The distribution, laterality and presenting vision of CAM patients with orbital apex syndrome LP: Light perception; FC: Finger count.

RESULTS

Among 89 patients of CAM 34.8% patients were found to have orbital apex syndrome. Among the patients presenting with involvement of orbital apex, males were predominant (61.2%, Chi-square: 4.8, P=0.03). Mean age of those patients was 56.5±1.2y (range 34-71y). All patients were found to have recent history COVID-19 infection. Majority patients had pre-existing diabetes mellitus. Rest were found to have COVID-19 infection associated hyperglycemia (25.8%). Eighteen 58% patients with orbital apex syndrome had received steroid as a treatment modality for COVID-19 infection (relative risk: 2.06, odds ratio: 2.89; P<0.05). Majority patients with orbital apex involvement were found to have no perception of light vision at presentation (61.8%).

Clinically, all patients with orbital apex syndrome presented with severe blepharoptosis. The 90.3% patients had complete ophthalmoplegia, 71.0% patients had mild degree of proptosis. Mean proptosis was found to be 22.3±0.2 mm (range: 21.2-22.8 mm); 90% of the proptosis was found to be axial in nature, 48.4% patients have central retinal artery occlusion (CRAO) in posterior segment of eye where as 25.8 % patients had significant optic disc oedema. Only 16.1 % patients with orbital apex involvement were found to have concurrent ocular adnexal tissue discoloration and necrosis. Three (9.7%) patients had bilateral orbital apex involvement (Figure 2).

MRI findings of all patients with orbital apex syndrome showed bony necrosis of the medial orbital wall and floor with involvement of maxillary and ethmoidal sinuses. Six patients (19.4%) had involvement of pterygopalatine fossa and cavernous sinus. Two patients with bilateral involvement showed variable patterns of brain parenchyma involvement

Table 1 The various treatment modalities for CAM patients with orbital apex syndrome

Laterality	BCVA	Treatment modality	*n* (%)
Unilateral (*n*=28)	No LP eyes	External debridement of paranasal sinuses with eyelid involving orbital exenteration	4 (12.9)
		Endoscopic paranasal sinus debridement with eyelid sparing orbital exenteration	10 (32.2)
		Endoscopic paranasal sinuses and orbital debridement (globe retaining)	9 (29.1)
	LP or better eyes	Endoscopic paranasal sinuses and orbital debridement (globe retaining)	5 (16.2)
Bilateral (*n*=3)	OU: no LP	Bilateral Eyelid involving orbital exenteration with right sided external paranasal sinus debridement	1 (3.2)
	OD: no LP OS: FC+	OD: endoscopic paranasal sinus debridement with eyelid sparing orbital exenteration OS: endoscopic paranasal sinuses and orbital debridement (globe retaining)	1 (3.2)
	OD: FC+ OS: no LP	OD: endoscopic paranasal sinuses and orbital debridement (globe retaining) OS: endoscopic paranasal sinus involvement with eyelid sparing orbital exenteration	1 (3.2)

BCVA: Best-corrected visual acuity; LP: Light perception; FC: Finger count; +: Positive.

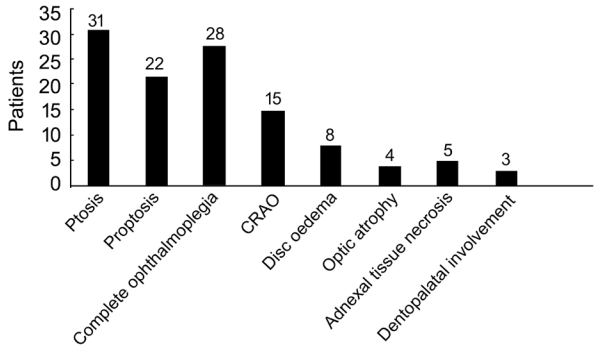

Figure 2 Spectrum of clinical presentation of CAM patients with orbital apex syndrome CRAO: Central retinal artery occlusion.

with necrosis of cribriform plate and ethmoidal sinuses.

Among patients who had unilateral involvement, 10 patients (32.3%) had undergone endoscopic debridement of involved paranasal sinuses with eyelid sparing orbital exenteration, followed by 9 (29.0%) patients who underwent endoscopic paranasal sinus and orbital debridement with preservation of eyeball. Five patients (16.1%) with preserved vision also underwent eyeball retaining endoscopic debridement of involved paranasal sinuses and orbit. One patient (3.2%) with bilateral involvement had undergone bilateral lid involving exenteration with open maxillectomy (Table 1).

All patients were found to have biopsy proven mucormycosis. But only 12 (38.7%) were positive in culture.

One month follow up out of 7 eyes which had finger count (FC) close to face vision at presentation, 2 eyes have improved to best-corrected visual acuity (BCVA) of 1.0 logMAR and one eye has improved to 0.8 logMAR. All such patients had undergone endoscopic sinus and orbital debridement. One patient with endoscopic paranasal sinus debridement and eyelid sparing orbital exenteration have developed sino-orbito cutaneous fistula. One patient with bilateral involvement who underwent bilateral eyelid involving orbital exenteration with right sided external paranasal sinus debridement was found to have microbiological recurrence from the orbits and sinuses. However, the patient could not undergo further operative intervention due to poor hemodynamic status and ultimately succumbed to the disease.

DISCUSSION

The prevalence of ROCM was quite rare in the pre-pandemic world. Yet it is known to have high rates of morbidity and mortality. The most common predisposing factor for the disease is poorly controlled diabetes mellitus. This is considered to be an opportunistic infection caused by *Mucorales* order of fungi[2]. Only 2%-6% of invasive fungal infections were attributed to *Mucorales* order in pre-pandemic times. Among solid organ transplant recipients, the cumulative incidence of mucormycosis before the pandemic situation was only 0.07% at the end of first year[5].

With the progress of the COVID-19 pandemic situation there is an increasing incidence of CAM specially among patients with uncontrolled hyperglycemia in the Indian subcontinent and elsewhere[6-8]. The soaring second wave of COVID-19 infection was found to be associated with exponential increase in the incidence of CAM[9-10].

Sheldon and Bauer[11] had shown that the expression of disease severity of mucormycosis was much more among metabolically abnormal rabbits as compared to metabolically normal rabbits' way back in 1959. The authors documented same inflammatory response pattern between the two groups of rabbits. But the onset, intensity and extent of the inflammation associated morphological changes in the tissue was strikingly more rapid and severe among the metabolically abnormal rabbits. They attributed these findings to the fact that uncontrolled hyperglycemia diminishes the normal granulocytic response to the fungal infection. Similar reasoning was given by Waldorf *et al*[12] in the murine model. They also attributed the findings to uncontrolled diabetes induced reduced bronchoalveolar macrophage response to the germinating spores. From past studies it becomes clear that however rare the incidence of ROCM was, it was definitely

more severe in disease expression among patients with uncontrolled hyperglycemia.

In the pyramid shaped orbit, the apex has a complex disposition of bone, nerves, soft tissue and vessels. Orbital apex syndrome refers to a constellation of ophthalmic manifestations associated with inflammation of orbital apex[13]. Most common cause of orbital apex involvement is immune mediated vasculitis[14-15]. Infective causes are mostly due bacterial infiltration into the orbit from surrounding paranasal sinuses[16]. Rarely, immunocompromised individuals had reported with orbital apex syndrome due to fungal etiology, mostly *Aspergillus* and *Mucor*[17]. The rapid onset and progression of fungal infection from paranasal sinuses into the orbit has been attributed to their angioinvasive nature[18].

In a study conducted by Jiang *et al*[17] the authors reported 11 cases of orbital apex syndrome associated with ROCM in pre-COVID era. Most patients were associated with uncontrolled diabetes mellitus and all cases were severely immunocompromised. All patients had undergone endoscopic debridement of necrotic tissue. Three patients had trans-ethmoidal optic nerve decompression. All patients were peri-operatively treated with intravenous amphotericin B. Yet only three patients survived. This study clearly points the invasive nature of *Mucor* infection in immunocompromised persons and also demonstrates the fatality associated with such infection[17].

The present study documents a reflection of the sudden surge of CAM with the furious second wave of COVID-19 pandemic in the Indian sub-continent. Among 89 CAM patients, the present study shows that the prevalence of orbital apex involvement is as high as 34.8% on presentation. This is quite alarming in the present setting of the pandemic situation in terms of patient morbidity and mortality. The 74.2% of patients with CAM and orbital apex syndrome had no LP. This clearly shows that patients with CAM are more prone to develop orbital apex involvement and subsequently have permanent loss of vision. The angio invasive spread of the fungi in the setting of COVID associated hyperglycemia is the principal reason for such scenarios.

The authors have no scientific explanation to attribute to the male gender preponderance of the CAM associated orbital apex involvement. The 25.8% of the CAM associated orbital apex syndrome patients had no past history of diabetes. They developed hyperglycemia associated with the COVID-19 infection. Use of steroid in the treatment of COVID-19 infection may have further augmented the prevalence of poorly controlled glycemic status. On comparison between CAM patients who developed orbital apex syndrome with those CAM patients who did not develop the same, history of steroid use was found to be a risk factor. However, the sample is quite small to arrive at a firm conclusion.

The coexistence of ptosis and proptosis among patients with CAM associated orbital apex syndrome can be perplexing at the outset. Logical and scientific explanation for that is plausible. The orbital apex involvement causes third nerve paralysis leading to ptosis. The co-existent proptosis is mostly mild in nature and is attributed to necrotic debris accumulation in orbital apex. Significant proptosis has not been documented in CAM associated orbital apex syndrome patients because of two reasons. First, orbital debridement of necrotic tissue has been done in most cases promptly on radiological diagnosis as a life-saving procedure and also for histopathological confirmation. Second, unlike noninfective and bacterial causes of orbital apex syndrome, *Mucor* quickly spreads intracranially before significant deposition of necrotic tissue leading to proptosis[3].

Significant prevalence of CRAO among CAM associated orbital apex syndrome patients also supports the angiogenic spread of the fungi. *Mucor* has a predilection to invade the internal elastic lamina of the blood vessels[3].

Radiologically, 19.3% of patients showed involvement of cavernous sinus in the present study. This is also firm evidence of the comparatively rapid spread of CAM in the setting of poorly controlled glycemic status. Partial or total bony destruction of the floor and medial wall with significant involvement of the orbital apex was evidenced in all cases of CAM associated orbital apex syndrome. Bilateral involvement with brain parenchyma infarction was also the presenting finding in 3 patients. In Figure 3 there is left optic nerve compression in contrast enhanced T1 contrast axial MRI of one of the patients. These radiological findings show the highly invasive nature of the fungus. All patients showed fungal isolation in histopathology as well as on Potassium hydroxide (KOH) mount in contrast only 38.7% showed culture positivity. This may be due to the fact mucoralae order of fungi are difficult to grow in culture media. About 50% of the samples are usually culture negative[4].

While managing cases with CAM associated orbital apex syndrome, the unanimous policy of the treating team was first to priotize saving life, then to save the anatomical integrity of the orbit with preserving the eyeball and lastly if possible preserving vision as far and as much as possible. Most patients with no involvement of the external facial skin and ocular adnexa had under gone endoscopic debridement of the sinuses with endoscope guided debridement of the orbit preserving the eyeball and eyelids. The debridement was followed with local infiltration of amphotericin B both in the affected sinuses and orbit. In one month follow up these patients had faster and cosmetically most satisfying outcome. Concurrent systemic amphotericin B administration perioperatively had in 38.7% cases preserved the presenting vision. The authors attribute

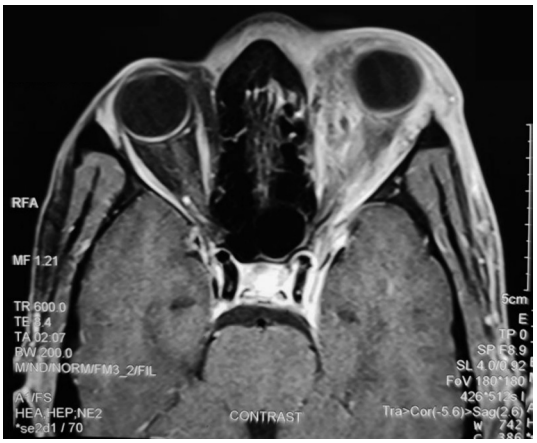

Figure 3 T1 contrast axial MRI image demonstrating contrast enhancement of extraconal part of left orbit with compression of left optic nerve.

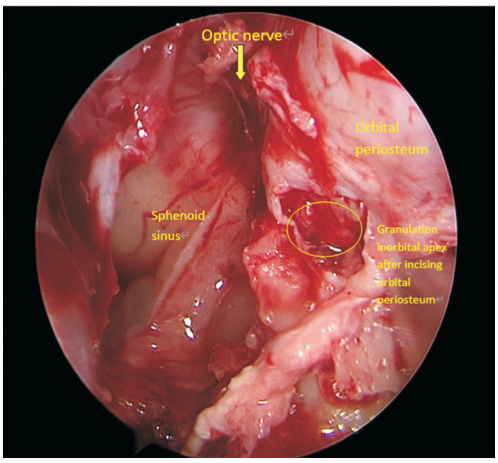

Figure 4 Endoscopic orbital debridement through medial orbital wall.

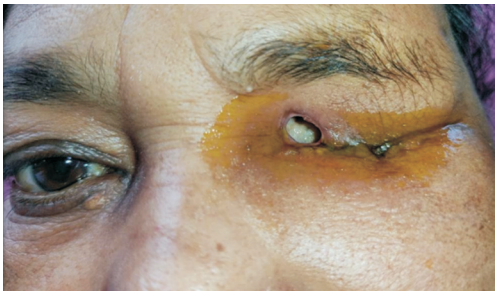

Figure 5 Post exenteration sino-orbito-cutaneous fistula formation in a patient.

this outcome to prompt diagnosis of the disease and early intervention.

Eyes with no LP and no facio-palatal and ocular adnexal necrosis underwent endoscopic sinus debridement with eyelid sparing limited orbital exenteration. Figure 4 demonstrates the maxillo-orbital structures of such a patient during endoscopic debridement in one-month post-operative period none has developed significant signs of contracted socket. This is attributed to conformer placement in the fornix. These patients have been planned for mucocutaneous grafting in the orbit with orbital prosthesis placement for a gratifying cosmetic outcome for the patients. Only one patient with lid sparing exenteration with endoscopic debridement developed sino-orbito-cutaneous fistula which is shown in Figure 5.

For those patients who had undergone external debridement of maxillary sinus with eyelid involving orbital exenteration had significant palato-facial and ocular adnexal necrosis. One patient with bilateral involvement and no LP had to undergo bilateral exenteration as a life saving measure. The cosmetic outcome in such patients will be difficult to accept and long-term rehabilitation will also be complicated.

It was astonishing to document that development of orbital apex syndrome took very little time in most patients from the time of onset of first symptoms like nasal stuffiness and repugnant discharge. In the present situation of COVID-19 infection waves, treating physicians need a strong suspicion for CAM. Early diagnosis and prompt intervention both surgical and medical, can not only reduce mortality but also preserve effective vision and spare the patient from lifelong cosmetic blemish.

For those eyes where presenting vision was better than LP, three patients were found to have improved vision up to 0.8 logMAR. These patients presented early and had undergone endoscopic paranasal sinus and orbit debridement. This clearly demonstrates that early diagnosis and prompt intervention can preserve useful vision in the eyes in CAM patients.

The authors intend to present this as a pilot study. With further cases being reported, longitudinal study with greater sample size and larger follow up period can more firmly substantiate the facts raised in this study.

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