



BLIND-SIDED BY BLACK FUNGUS: CRAO IN CAM

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ABSTRACT

Importance: There has been an outbreak of COVID-19 associated rhino-orbito-cerebral mucormycosis (CAM) in many parts of developing world. The clinical profile, mortality rate, risk factors associated with it has been studied. A case series highlighting association of Central Retinal Artery Occlusion (CRAO) in CAM has not been reported yet. **Objective:** To report a case series of Central Retinal Artery Occlusion (CRAO) in 15 patients with history of COVID-19 infection associated mucormycosis (CAM). **Design:** This is a retrospective observational study of 15 cases of rhino-cerebro-orbital mucormycosis (ROCM) which presented to our tertiary referral centre between March 2021 and June 2021. All patients had unilateral or bilateral CRAO. **Setting:** Tertiary care multispecialty hospital in western India. **Participants:** All patients diagnosed with CAM and having unilateral or bilateral CRAO. Main outcome measure: The COVID-19 disease induced inflammatory homeostasis changes that predispose to thrombotic disease in both venous and arterial circulation in CAM. Overall prognosis appears to be poor with mortality rate of 14- 50% in various studies. **Results:** Fifteen patients were studied of which 13 were male and rest females. The mean age of patients was 55.6 + 12.13 years (Range: 39 –78 years). Majority had uncontrolled Type 2 Diabetes Mellitus. Tissue and radiological diagnosis of mucormycosis was made in all patients. Twelve patients had unilateral CRAO and 3 patients had bilateral CRAO. **Conclusions and relevance:** Diabetes and systemic steroids have proven to be risk factors for development of CRAO in CAM. Early ophthalmic screening should be initiated in COVID-19 patients with systemic co-morbidities, to reduce the immediate and late sequelae.

KEYWORDS : CAM, CRAO, Covid-19, ROCM, Mucormycosis

INTRODUCTION

Till date, COVID-19 infection has afflicted over 298 million people worldwide with more than 5.4 million people succumbing to disease. In India, 35 million people have been afflicted with over 4.5 lakhs people succumbing to death.

A recent upsurge in the cases of mucormycosis has been evident during the resurgence of COVID-19 pandemic. This has given rise to a syndemic named called COVID-19 associated rhino-orbito-cerebral mucormycosis (CAM).^[1]

The sequelae of COVID-19 are more severe and are related to systemic inflammation. It leads to coagulopathy causing direct damage to blood vessels, with hepatic, renal and cardiac injuries.^[2]

There is complement mediated thrombotic micro angiopathies (TMA), rather than sepsis induced coagulopathy or disseminated intravascular coagulation (DIC).^[3] This leads to endothelial damage and microvascular thrombosis.^[4]

Mucormycosis is a life-threatening, opportunistic infection. Patients with moderate to severe COVID-19 disease are more susceptible to it because of the compromised immune system. Diabetes mellitus (DM) and use of immunosuppressive

therapy (corticosteroids) are additional risk factors for development of CAM.^[5,6,7] Mortality rate in CAM is more than 50% even after initiating treatment.^[8]

The pathogenesis of retinal artery occlusion (RAO) is a multifactorial process where inflammatory and hyper coagulable state are established risk factors.^[9] However, the effects of COVID-19 inflammatory and pro-coagulant state over the retinal vascular system have not been investigated yet. Our study aims to identify the risk factors and outcomes associated with development of Central retinal artery occlusion (CRAO) in CAM.

MATERIAL AND METHODS

This is a retrospective observational study of 15 cases of CAM who presented to our department between March 2021 and June 2021. It was in accordance with the ethical standards as mentioned in the amended Helsinki Declaration.

These patients were treated at tertiary care hospital with multidisciplinary approach. Patients presented with one or more of the following symptoms; sudden loss of vision, drooping of upper eyelid, swelling over cheek and face.

The patients either had active COVID-19 infection or had recent history of same. All cases were treated with

corticosteroids as a standard treatment protocol for COVID-19.⁽¹⁰⁾ Patient's demographic data, clinical manifestations and underlying systemic conditions were analysed. Comprehensive ophthalmologic evaluation, otolaryngeal and neurological examination, microbiological and radiological records was assessed to determine disease extent and severity.

CRAO is a component of orbital apex syndrome which is defined as simultaneous dysfunction of optic nerve and other cranial nerves presenting with vision loss, ptosis, fixed and dilated pupil, complete internal and external ophthalmoplegia (Figure 1). A detailed ophthalmic evaluation and fundus photography was done for documentation.



Figure 1: Clinical photograph showing complete Ptosis, facial swelling on right side of face.

Tissue diagnosis was made on KOH mount. Based on CT and MRI findings of paranasal sinuses, orbit and brain, the extent and staging of disease was documented (Figure 2).

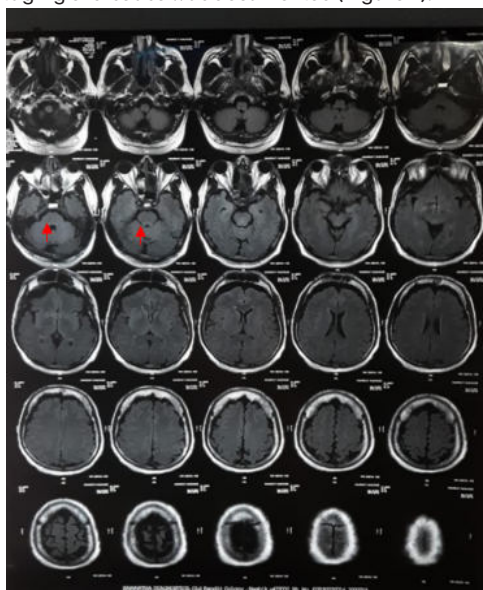


Figure 2: MRI scan showing bilateral involvement of orbit and paranasal sinuses.

Diabetes was controlled with medical management. All patients received systemic and few patients received retrobulbar amphotericin (intraconal) injection. The systemic dose was 1.0 mg/kg/day increasing to 2.5 to 3g. Retrobulbar injection dose was 1ml of 3.5 mg/ml. Retrobulbar administration was repeated after assessing the clinical condition and response to the treatment.

The outcome of treatment was assessed in terms of treatment success and failure. Treatment success was defined as a stable and disease-free patient. Treatment failure was defined as case fatality following confirmed diagnosis of CAM. Due to COVID-19 active infection and/or critical systemic condition of patients, some of the diagnostic ophthalmic modalities could not be performed.

RESULTS

This retrospective study included 15 patients of mucormycosis who developed CRAO. The mean age of patients was 55.6 ± 12.13 years. (Range: 39 – 78 years). Majority 13 (86.7%) were males. One case had completed both doses of covid vaccination while the rest were unvaccinated. Other baseline characteristics have been represented in table 1.

Table 1: Baseline characteristics in patients who developed CRAO (N = 15)

Variable		Number of patients
Current Covid Status (N, %)	Positive	11 (73.3%)
	Negative	4 (26.7%)
HRCT score at onset (mean ± S.D)		9.8 ± 2.98 (5-15)
Covid severity score (CT -Score)	CT Score 6	5 (33.33%)
	5	9(60%)
	2	1(6.66%)
Severity of COVID	Home care, Ambulatory	1 (6.7%)
	Hospitalized and on O2	9 (60%)
	Hospitalized, on O2 BiPAP	5 (33.3%)
O2 Saturation	<90%	1 (6.7%)
	90-95%	3(20%)
	>95%	11(73.3%)
Comorbidities	Diabetes Mellitus	15 (100%)
	Hypertension	13 (86.7%)
	Chronic Kidney disease	3 (20%)
	Alcoholic liver disease	1 (6.7%)
	Chronic Alcoholism	1 (6.7%)
	HbsAg positive	1 (6.7%)

Most common comorbidity was uncontrolled DM (all cases), of which two were diagnosed upon admission. Three (20%) patients were on oral hypoglycaemic agents (OHA), another 10 (66.7%) were on insulin and rest (13.3%) were taking both. Treatment details are given in table 2. Average number of days since the diagnosis of covid was 23.87 ± 11.20 (Range 4-43) for development of CAM.

Table 2: Treatment details

Treatment details	Number	Percent	Mean duration (days)
Intravenous (I.V.) steroids	15	100%	9.4 ± 4.28 (4-16)
Oral steroids	2	13.3%	6.5 ± 2.12
Remdesivir	7	46.7%	5 ± 0.81(4-6)
O2 mask	12	80%	15 ± 1.12 (10-25)
O2 Ventilator	2	13.3%	11 ± 4 (7-15)
Retrobulbar amphotericin B	9	60%	-
Intravenous amphotericin B	15	100%	12 ± 1.82 (2-25)
FESS (Functional endoscopic sinus surgery)	15	100%	-
Exenteration	2	13.3%	-
Survival	6	40%	
Death	9	60%	

Clinical details:

The general condition was poor in 2 cases (13.3%). The most common presenting symptoms were drooping of eyelid in 6 (40%) cases, sudden loss of vision in 5 (33.33%), facial swelling in 2 (13.33%) cases and ecchymosis around eye in

one (6.7%) case. Ptosis was noted in majority of the group (7 cases, 46.66 %), followed by periorbital/ocular oedema (4 cases, 26.7%), nasal ulcer (2 cases, 13.3%), proptosis and nasal discharge (1 case each, 6.7%).

Visual acuity was PL negative in all the cases in affected eyes. Reason for loss of vision was CRAO in all cases. Left eye was involved in 8 patients. Right eye was involved in 4 patients while three patients had bilateral involvement.

Diagnosis:

Diagnostic Nasal Endoscopy (DNE) was performed in 14 (93.3%) cases. Commonly used sample was nasal crust in 13 (86.7%) cases, followed by nasal mucosal biopsy in 2 (13.3%) cases. KOH mount showed septate hyphae in all cases. Radiological diagnosis for extension and staging of ROCM was done as per code mucer.^[11] Covid severity score (CT-Score) was in the range of 2-6. (Table 1)^[12]. HRCT score was moderate in all patients.^[13]

Management:

Systemic amphotericin B was given in all cases for treatment of ROCM. FESS was done in 12 (80%) cases and was combined with exenteration in two cases. Retrobulbar amphotericin B was given to 9 (60%) cases, of which two received single dose, 6 received alternate day 3 doses and one received 3 doses with variable frequency.

Outcome:

Six patients survived, while 9 had a terminal outcome.

DISCUSSION

Mucormycosis is a rare and lethal fungal infection caused by the Mucoraceae family, belonging to Phycomycetes or Zygomycetes class.^[14, 15] It is a commensal of the nasal mucosa. However, it rapidly proliferates in nasal cavity and paranasal sinuses (PNS) of immunosuppressed patients.

The incidence of mucormycosis is not age or gender dependent. The significantly higher number of males in this study may be a reflection of higher Covid-19 prevalence in males.^[16]

In diabetic individuals, there is an imbalance between clotting factors and fibrinolysis which may lead to increased risk of thromboembolic events.^[17] All patients in our study had DM while Muthu et al.^[18] and Sen et al.^[19] reported DM in 66 % and 78 % of their respective patients.

All patients in our study were treated with steroids,^[10] while it was 87% in the study of Sen et al.^[19]

Corticosteroids are strong anti-inflammatory agents and are used in treating immunologic complications of COVID-19 infection.^[20-21] Systemic steroids cause fluctuating blood glucose levels and may contribute to occurrence of mucormycosis in COVID-19 patients.^[22] Inadvertent use of steroids was independently associated with COVID-19-associated mucormycosis.^[1] Literature has shown that corticosteroid treatment was linked with higher mortality rates associated with ROCM.

Our case series showed 60% mortality rate in CAM. The prognosis of CAM is poor with the overall mortality rate of 14-50% in various studies.^[18,19,23,24]

The risk of thromboembolic events in COVID-19 patients is currently under investigation. Preliminary results showed significantly prolonged prothrombin time, high D-dimer levels and increased concentrations of pro-inflammatory cytokines.^[25] Patients with severe disease show higher level of these inflammatory biomarkers possibly indicating disseminated

intravascular coagulation (DIC) or thrombotic microangiopathy.^[26] Most cases have venous thromboembolism, but there are increasing reports of COVID-19 induced arterial thromboembolic complications, pointing to high thrombogenicity of SARS-CoV-2 infection.^[27,28]

CRAO is now an established ophthalmic complication of COVID-19 that can lead to permanent vision loss.^[29-31] Mucormycosis can cause ciliary as well as central retinal artery occlusion.^[23] The post-mortem analysis revealed direct viral infection of endothelial cells and diffuse endothelial inflammation which is suggestive of CRAO.^[33]

ROCM with CRAO points towards development of orbital apex syndrome. Early execution of orbital exenteration may reduce intracranial spread and subsequent mortality. Repeated surgical debridement may be needed for local control of the disease. An aggressive surgical approach seems to improve patient survival. Once the disease is suspected, all immunosuppressive agents should be tapered or discontinued. Antifungal therapy must be initiated immediately.^[34]

We are the first to report case series of 15 patients who developed CRAO in CAM from a single centre. Due to unknown mechanism of CRAO in such patients, traditional treatment modalities may not be effective. Hence, there is a need to define treatment protocol for CRAO in CAM.

The retrospective observational nature of the study with small number of patients may be a short coming of our study. The statistical significance of the findings needs to be established by a well-designed experimental study.

CONCLUSION

Uncontrolled diabetes and injudicious use of corticosteroids have proven to be risk factors for CAM. These patients need close ophthalmic monitoring for early diagnosis of CRAO. Prompt initiation of systemic antifungals and aggressive surgical intervention after early diagnosis of ROCM may attenuate the intracranial spread and mortality of this fatal disease.

Conflicts of Interest & Financial disclosure:

None of the authors have any financial/ conflicting interests to disclose.

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Data Availability:

On request, data can be made available. Corresponding author has full access to all the data in the study and takes responsibility for the integrity of the data and the accuracy of the data analysis.

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