Original Article

Central Retinal Artery Occlusion in COVID-Associated Mucormycosis

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Abstract

Introduction: Significant surge of mucormycosis was reported in the Indian Subcontinent during the second wave of the COVID-19 pandemic. COVID-associated mucormycosis (CAM) was defined as the development of features of mucormycosis with prior or current history of COVID-19 infection. Rapid angioinvasion is an important characteristic of mucormycosis. Authors intended to find out the prevalence of retinal arterial occlusion and its association with vascular embolic occlusion elsewhere in the body among CAM patients in this study. **Methods:** This was an observational study. All consecutive-confirmed cases of mucormycosis (n = 89) and age-/gender-/risk factor-matched controls (n = 324) admitted in the designated COVID center were included in the study. All cases and controls underwent comprehensive ophthalmological, otorhinological, and neurological examinations. All necessary investigations to support the clinical diagnosis were done. Qualitative data were analyzed using the Chi-square test. Quantitative data for comparison of means between the cases and controls were done using unpaired t-test. **Results:** Twenty-one (23.59%) patients manifested the defined outcome of central retinal artery occlusion (CRAO). Among age-matched control, with similar diabetic status, none had developed the final outcome as defined ($P < 0.05$). About 90.47% of subjects with CRAO presented with no perception of light vision. Thirteen subjects (61.9%) with the final outcome developed clinical manifestations of stroke during the course of their illness with radiological evidence of watershed infarction ($P = 0.001$). Orbital debridement was performed in 9 (42.85%) subjects while orbital exenteration was done in 8 (38.09%) subjects. **Conclusions:** CRAO in CAM patients was found to have aggressive nature turning the eye blind in a very short period of time. CRAO can serve as a harbinger for subsequent development of more debilitating and life-threatening conditions such as stroke among CAM patients.

Keywords: Central retinal artery occlusion, COVID-associated mucormycosis, stroke, watershed infarction

Introduction

A significant surge of invasive fungal diseases was reported in the Indian Subcontinent during the second wave of the COVID-19 pandemic. This can be attributed to a number of factors such as diabetes, widespread use of steroids, increased antibiotic use, or some, yet to be known intriguing factors.[1] Mucormycosis is the second most common invasive fungal disease to affect the human population following aspergillosis. It was usually seen in the background of immunosuppression such as poorly controlled diabetes, hematological malignancies, and solid organ transplantation.[1-3]

Angioinvasion is an important characteristic of mucormycosis. This causes rapid invasion of the fungus in the body. Most commonly this fungus invades the paranasal sinuses from the nose and ultimately reaches brain through orbit. This is known as rhino-orbito-cerebral mucormycosis (ROCM). Gastrointestinal, renal, pulmonary, and cutaneous mucormycosis is also reported in various literature. COVID-associated mucormycosis (CAM) was defined as the development of features of mucormycosis with prior or current history of COVID-19 infection. If ROCM

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is developing within 7 days of COVID infection, then it is called early CAM. If ROCM is developing 8 days or later up to 8 weeks following diagnosis of COVID-19 disease, then it is referred as late CAM.[1,4]

Mucormycosis can lead to a wide array of ophthalmological manifestations in the form of conjunctival congestion, ptosis, proptosis, and diminution of vision owing to the involvement of the anterior or posterior chamber, optic nerve, sheath, and/or retinal vascular occlusion. Extraocular muscle involvement frequently leads to ophthalmoplegia.[5]

The optic disc or papilla is the ophthalmoscopically visible tip of the intraocular portion of the optic nerve. The nerve head is a vertical ellipse and appears pinkish to yellowish-white. The ophthalmic artery and some filaments of the sympathetic carotid plexus accompany the nerve through the optic canal, within the same dural sheath. About 8–12 mm posterior to the globe, the artery enters the optic nerve and runs along its center to the optic disc, where it becomes the central retinal artery.[5,6]

Since angioinvasion plays a key role in the spread of mucormycosis, central retinal artery occlusion (CRAO) might have been one of the significant factors leading to sudden irreversible loss of vision in CAM patients. The authors intended to find out the prevalence of retinal arterial occlusion and its association with vascular embolic occlusion elsewhere in the body among CAM patients.

Methods

This observational study was conducted from May 2021 to July 2021 at a tertiary care referral-based institute, declared as apex hub for the management of mucormycosis. All consecutive-confirmed cases of mucormycosis (n = 89) and age-/gender-/risk factor-matched controls (n = 324) admitted in the designated COVID center for the same institute were included in the study.

CRAO (International Classification of Disease-10 Code: H: 34.1) is defined as:

1. Sudden profound loss of vision (monocular or binocular)
2. Associated relative afferent pupillary defect (RAPD) in the affected eye
3. On fundus evaluation, any two of the following apart from pale edematous ischemic retina:
    a. Cherry red spot in macula
    b. Retinal arteriolar attenuation with segmentation of blood
    c. Identification of the site of embolization.

Cases were defined as subjects in whom mucormycosis was confirmed with clinical manifestations, radiological evidence of invasive fungal disease, and demonstration of fungus in tissue specimen by the presence of broad aseptate or pauci-septate hyphae with wide angle branching and evidence of tissue invasion (potassium hydroxide mount/histopathological examination [HPE]). Controls were defined as age-, gender-, and risk factor-matched subjects with COVID-19 disease requiring hospital admission during the study interval.

All cases and controls underwent comprehensive ophthalmological, otorhinological, and neurological examinations. All necessary investigations to support the clinical diagnosis were done. The subjects underwent treatment in the form of clearance/tissue debridement surgery of the sinus, orbital floor clearance, or debulking or exenteration (depending on the amount of tissue invasion and visual acuity of the involved eye of the patient). The subjects also received injectable amphotericin B at 1 mg/kg body weight for 21 days, followed by the tablet posaconazole 300 mg OD for 90 days. All the exenterated orbital specimens were subjected to HPE, with tissue being subjected to standard hematoxylin and eosin staining along with the use of Gomori's methenamine silver (GMS), periodic acid–Schiff stain. Prior written permission from the Institutional Ethics Committee was taken. The study was conducted maintaining the tenets of the Declaration of Helsinki, and the data were analyzed using the Chi-square test and unpaired t-test.

Results

The total cases during the study period were 89 (mean age of 54.67 ± 9.23 years), out of whom 21 (23.59%) patients manifested the defined outcome of CRAO. Among the affected, the mean age was 53.85 ± 9.49 with 13 males (61.9%) and 8 (38.1%) females. Sixteen subjects (76.1%) were previously known diabetics on treatment while 5 (23.9%) had developed diabetes as per the American Diabetes Association criteria postdevelopment of COVID-19 disease. Among age-matched control, with similar diabetic status, none had developed the final outcome as defined ($P < 0.05$). The mean age of the controls was 56.34 (±10.34) with, 60.4% subjects (n = 196) with type 2 diabetes mellitus ($P < 0.05$).

Out of 21 subjects with the final outcome (CRAO), perception of light was denied by 19 (90.47%) while in 2 (9.52%) subjects, finger counting was present. Among all the subjects who had developed CRAO manifested the clinical findings of proptosis of the affected eye were found in 8 (38.09%) with complete ophthalmoplegia being found in 15 (71.42%) and rest 9 (42.85%) having incomplete ophthalmoplegia with medial and inferior rectus palsy being most commonly documented. RAPD was found in 4 (19%) cases and the rest had fixed nonreacting pupils [Figure 1].

Majority of our patients with CAM presented with fundal pictures showing retinal edema, attenuation of retinal arteries, and pale macula with cherry red spots [Figure 2].

Orbital apex syndrome (in subjects with clinical suspicion and radiologic corroboration) was elicited in 13 (61.9%) subjects and 8 (38.09%) out of 21 subjects had clinicoradiological manifestations of cavernous sinus involvement [Figure 3]. Optic nerve sheath enhancement was found in 14 (66.66%) subjects. Digital fluorescence angiography (DFA) was done in 11 (52.4%) out of 21 patients as the rest (n = 10) were too

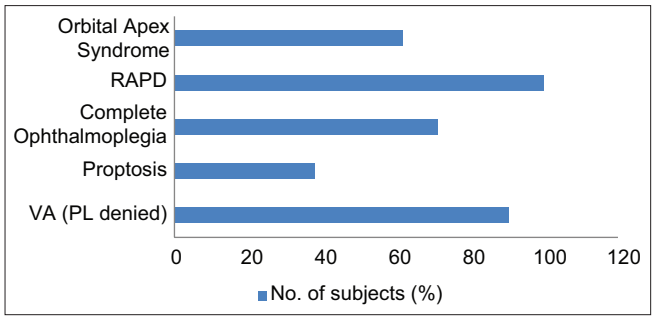

Figure 1: Features associated in subjects with outcome of CRAO. CRAO: Central retinal artery occlusion, RAPD: Relative afferent pupillary defect, VA: Visual acuity, PL: Perception of light

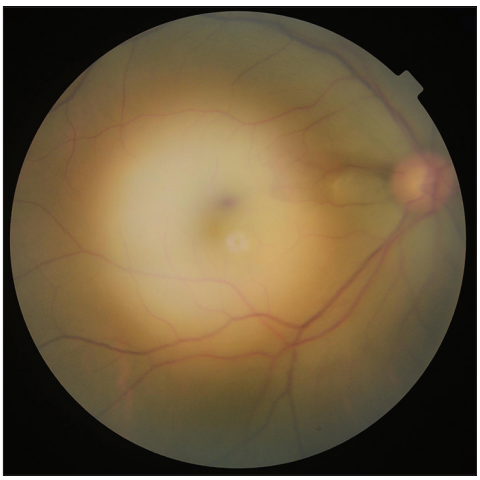

Figure 2: Color fundus image of right eye showing retinal edema, pale macula with cherry red spot, and attenuation of retinal arterioles (acute stage, on presentation), suggestive of central retinal artery occlusion

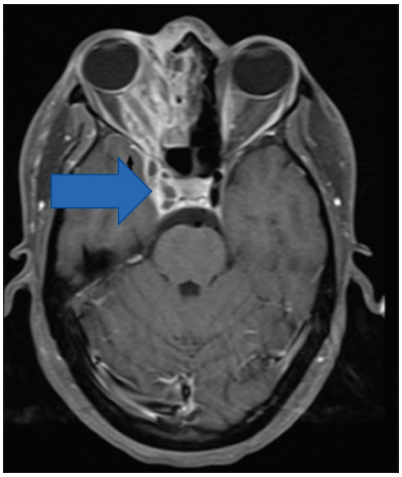

Figure 3: T1 weighted gadolinium contrast axial image of brain/orbit showing soft-tissue enhancement with optic nerve sheath enhancement, infiltration into the orbital apex (left) with involvement of cavernous sinus, destruction of medial orbital wall, and involvement of ethmoidal sinus. The Bblue arrow is pointing the thrombosed cavernous sinus

moribund for the examination or had deranged renal profiles. Seven subjects (63.6%) showed cattle trucking and delayed arterial filling [Figure 4]. On ocular coherence tomography out of 16 patients who were physically fit to undergo the scan, the mean central macular thickness was 312.6 ± 28.7 μ.

Thirteen subjects (61.9%) with final outcome developed clinical manifestations of stroke during the course of their illness which was corroborated radiologically. All the subjects who had developed stroke, had watershed infarction (superficial and deep territories of middle cerebral artery (MCA), [Figure 5] while 5 (23.8% of subjects with stroke) had watershed infarction between anterior (anterior cerebral artery [ACA]) and MCA or between posterior (posterior cerebral artery [PCA]) and MCA due to involvement of the internal carotid artery (ICA) by angioinvasion or vasospasm, ipsilateral to the side of CRAO [Figure 6].

Among patients of ROCM with manifestations of CRAO, undergoing surgical intervention, orbital debridement was performed in 9 (42.85%) subjects while orbital exenteration was done in 8 (38.09%) subjects. Among the exenterated tissue specimen undergoing biopsy angioinvasion was established in all (100%) by demonstration of broad aseptate/pauciseptate with wide angle branching hyphema within the central retinal artery, with the GMS stain at ×400 [Figure 7].

Discussion

Middle-aged (average age = 53.85) rural middle-class population with a male predominance (male: female = 1.6:1) were most commonly affected, reflecting the pattern of COVID-19 disease for greater affection of the male population.[1] All CAM patients had diabetes and 100% had features suggestive of COVID-19 disease with laboratory confirmation by reverse transcriptase–polymerase chain reaction method ($P < 0.05$). Steroid use was also found to be a risk factor for the development of CAM (77%, relative risk: 2.06, odds ratio: 2.89, $P = 0.001$). However, it was most prominently observed that the occurrence of multiple risk factors together increased the chances of CAM with diabetes being the most important. In a study where Yohai *et al*. analyzed the ophthalmic and nonophthalmic signs and symptoms during the course of ROCM, they found 60% of the subjects to be diabetic.[2]

ROCM causes a diminution of vision owing to a multitude of underlying factors. Optic nerve involvement may occur at multiple levels: Intraocular portion or intraorbital portion; either by direct infiltration or compression by extraocular muscles; and soft tissue. Intracanalicular or intracranial portion of the optic nerve involvement is associated with orbital apex syndrome and cavernous sinus thrombosis. This has been well documented in the present study.[5-8]

The retina is developmentally a part of the diencephalon and its blood supply is from ICA. The retinal vessels exhibit unique characteristics that can be directly and noninvasively examined during ophthalmoscopy. The most common established causes of CRAO are retinal embolism. Retinal embolism can be of three types: calcific, cholesterol, and platelet fibrin.[9]

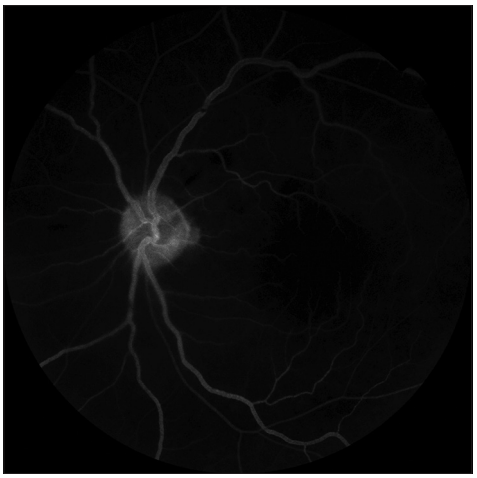

Figure 4: Digital fluorescence angiography showing delayed filling up of retinal vessel in left eye with cattle trucking appearance

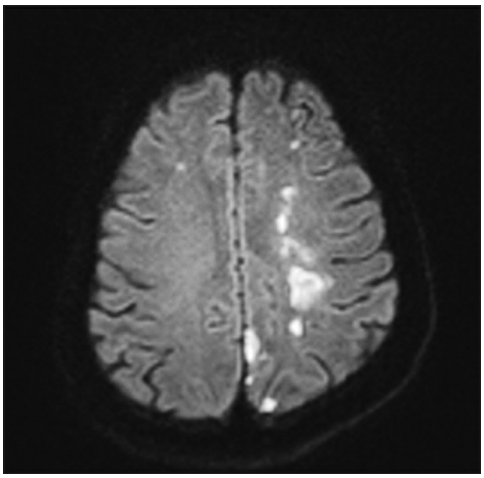

Figure 5: Diffusion-weighted magnetic resonance imaging image of coronal cut section of brain showing restriction in watershed zone of superficial and deep territories of left middle cerebral artery

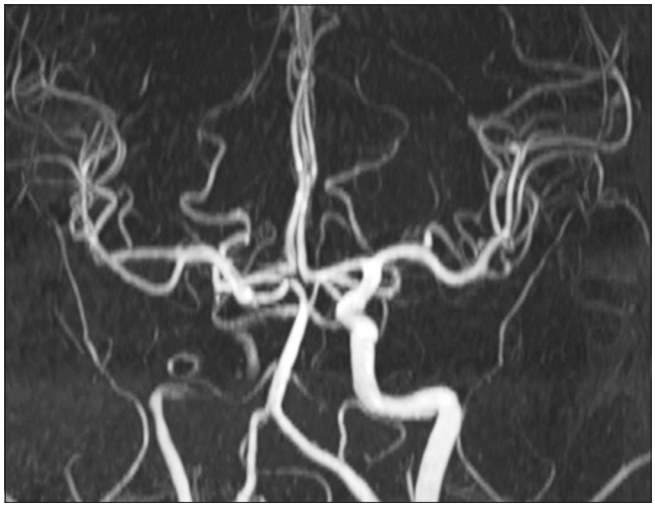

Figure 6: Magnetic resonance angiography of cerebral vessels showing filling defect (time of flight image) in cavernous part of right internal carotid artery

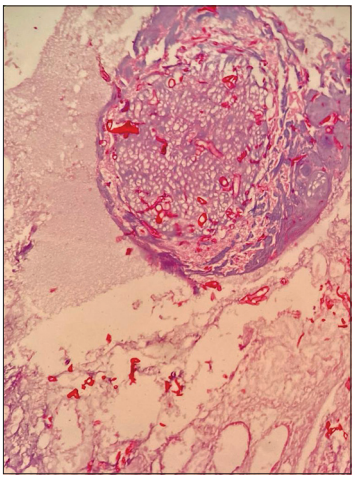

Figure 7: ×400 Gomori's methenamine silver stain highlights the mucorales (mucormycosis: Broad aseptate wide-angled branching hyphae) within the lumen of the central retinal artery

Mucormycosis is a known cause of central retinal and ciliary artery occlusion. Ferri and Abedi described an exenteration specimen of ROCM with thrombosed ciliary arteries.[8] Brown *et al*. reported one of eight and Bullock *et al*. one of two cases with acute retinal/choroidal artery obstruction, in mucormycosis (ROCM).[10,11]

CRAO in ROCM has an incidence of 16%–20%.[5] It is attributed to the direct infiltration of a central retinal artery by the fungus which is known to have a predilection for internal elastic lamina of blood vessels. This propensity of invading the internal elastic lamina leads to hemorrhagic necrosis of the vessel wall, thrombosis within the lumen of the vessel (preconditioning) for the development of distant embolism, vasospasm leading to transient distal hemodynamic compromise, and external compression causing decreased distal blood flow.[12]

In the study by Bhansali *et al*. on ROCM, vision loss was found in 80% of their cohort and 7 out of 35 had their vision loss attributed to CRAO.[5] In our study, 23.07% of the CAM cases had features suggestive of CRAO in concordance with previous studies. In cases of ROCM with loss of vision owing to CRAO, there is a simultaneous presence of pain from the involvement of other pain-sensitive structures such as the bony periosteum, extraocular muscles, surrounding paranasal sinuses, and involvement of meninges.[1]

In all cases of CAM with CRAO, magnetic resonance imaging orbit showed radiological evidence of orbital invasion by the fungus. The spread occurred by bone necrosis along the medial orbital wall mostly from the maxillary sinus and nasal cavity which were almost universally involved in our study population. Involvement of the cavernous sinus and orbital apex was found in 8 (38%) and 13 (62%) subjects, respectively, among cases with defined final outcomes, which was in concordance with previous studies.[1,4,6,7] The central retinal artery pierces the optic nerve sheath to run along the

substance of the optic nerve. In the total case population, optic nerve sheath enhancement was found 54 (59.34%) in subjects, out of which 14 (66.66%) developed CRAO, again substantiating direct angioinvasion in CAM as a cause of CRAO. Another aspect of this spectrum was the involvement of the cavernous part of the ICA as evidenced on magnetic resonance angiography brain in subjects who had developed CRAO.

The patients ($n = 11$, 52.4%) who were medically fit, underwent DFA. DFA revealed delayed arterial filling, reduced arterial caliber, and cattle trucking of blood column in seven.[13] Optical coherence tomography showed increased thickness of inner retina in the early phase of/CRAO due to retinal edema.[14]

All the exenterated tissue specimens underwent HPE which revealed angioinvasion by broad aseptate wide-angle branching fungus into the central retinal artery. This is definitive evidence of CRAO being a part of CAM due to angioinvasion by mucormycosis.[3]

An important observation was that 13 (61.9%) out of 21 subjects with CAM-associated CRAO progress to develop stroke in the form of watershed infarcts. Extension of mucormycosis from the intra-orbital compartment to the cavernous sinus occurs through superior orbital fissure or extension of sinus pathology to cavernous sinus. Involvement of cavernous portion of the ICA vis-à-vis external compression/thrombus *in situ*/vasospasm led to the propensity to develop stroke.[1,12,15] Most common sites of stroke were watershed infarcts between superficial and deep territories of MCA. All 13 (100% with stroke) patients in the present study showed the same locations of infarcts. However, 5 (23.8% with stroke) subjects also had watershed infarcts between ACA/MCA and MCA/PCA.

As the retina and the brain have a common blood supply from the ICA, any pathology affecting the ICA system can thus affect both. The large epidemiologic study of the Beaver Dam Eye Study, the pooled study of the Beaver Dam Eye Study, and the Blue Mountains Eye Study reported the association between retinal arteriolar emboli and incident stroke mortality. In a study, between 401 retinal artery occlusion subjects and 2003 sociodemographically matched comparison subjects, it was found that CRAO subjects exhibited a higher subsequent incidence of stroke during the 10-year follow-up after adjusting for hypertension/ischemic heart disease/atrial fibrillation/diabetes mellitus and dyslipidemia.[16] Hence, an association of CRAO as a predictor for stroke development is well established. Our study findings are also in concordance with the same.[15-18]

Since mucormycosis is a rapidly invasive disease and early treatment is imperative, CRAO can serve as a harbinger for subsequent development of more debilitating and life-threatening conditions such as stroke. More aggressive therapy is warranted in such cases.[19,20] However, COVID-19 disease has also been implicated as an independent factor for the development of vasculitis-induced CRAO. Yet, in our study, none of the control population had any features suggestive of CRAO in sharp contrast to CRAO being documented in 21 out of 89 subjects in CAM.[21] However, due to a lack of adequate data, the authors could not document the exact mean time interval between the onset of CAM and CRAO. This may be considered a major limitation of the present study.

Conclusions

CAM saw an enormous surge during and following the months of rising COVID-19 cases in India (during the second wave). The disease had devastating presentations with most of the cases being attributed to ROCM. One of the most devastating outcomes was the loss of vision owing to a multitude of factors, CRAO being one of the significant causes. CRAO in CAM patients was found to have aggressive nature turning the eye blind in a very short period of time. The risk of progression of ischemic stroke was also found to be much higher in such patients in comparison to earlier literature. The presence of CRAO served as an early marker for the subsequent development of stroke and thereby poorer outcome in terms of mortality and morbidity. Any CAM patient with dimness of vision requires urgent ophthalmological review for early detection of vascular occlusion. This will help to preserve vision as well as predict the risk of developing ischemic stroke or morbid vascular occlusion elsewhere in the body.

Research quality and ethics statement

This study was approved by the Institutional Review Board/Ethics Committee (IPGME and R Research Oversight Committee, memo no-IPGME and R/IEC/2021/546). The authors followed applicable EQUATOR Network (https://www.equator-network.org/) guidelines during the conduct of this research project.

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Nil.

Conflicts of interest

There are no conflicts of interest.

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