



CASE SERIES OF UNILATERAL CENTRAL RETINAL ARTERY OCCLUSION IN PATIENTS OF RHINO-ORBITAL-CEREBRAL MUCORMYCOSIS OCCURRING IN POST COVID DIABETIC PATIENTS.

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ABSTRACT **BACKGROUND** Rhino-orbital-cerebral Mucormycosis (ROCM) is an uncommon opportunistic and devastating fungal infection caused by filamentous fungi of the family Mucoraceae, typically affecting diabetic or immunocompromised individual. We are presenting a case series of four patients with unilateral central retinal artery occlusion (CRAO). On retrospective analysis of patients records, we found that all the patients had sudden painless loss of vision in one eye following symptoms of sinusitis, with common history of covid 19 infection in recent past, steroid intake, poorly controlled diabetes mellitus and raised serum ferritin level. Magnetic Resonance Imaging scan revealed Pansinusitis with orbital involvement and intracranial spread of disease in some of the patients. Urgent debridement of paranasal sinuses was done. Histopathological examination revealed broad based, filamentous, aseptate hyphae suggestive of mucormycosis. All the patients received similar treatment with intravenous and retrobulbar injection of Amphotericin B with local debridement. Clinical improvement was observed in few weeks with gradual resolution of ptosis and ocular movement, however, the involved eye remained blind following the CRAO and that could not be reversed.

KEYWORDS : rhino-orbital-cerebral mucormycosis, central retinal artery occlusion, diabetes mellitus.

CASE PRESENTATION

In this study, four post covid diabetic patients were presented who suffered from Rhino-orbital-cerebral Mucormycosis and unilateral central retinal artery occlusion (CRAO).

The etiological agent of Mucormycosis was isolated and identified by sequence analysis and data were registered in gene bank data base.

INTRODUCTION

Rhino-orbital-cerebral Mucormycosis is a lethal opportunistic fungal infection with acute and fulminant manifestation, typically affecting diabetic or immunocompromised patients.⁽¹⁾ It is caused by filamentous fungus belonging to family Mucoraceae.

Among Mucoraceae *Rhizopus oryzae* is the most common causative agent. Its incidence is high in diabetic patients due to greater availability of glucose to the pathogen. Lower pH in diabetic ketoacidosis, show reduced serum inhibitory activity against *Rhizopus*, lower response of T-cell, reduced phagocytic activity of macrophages and increased availability of free serum iron, which aid in growth of fungus.⁽²⁾ Mode of infection is inhalational route, through which fungal spores enter and grow in nasal and paranasal sinuses mucosa and because of its invasive nature it shows a contiguous spread to neighboring tissues including orbit and brain.⁽³⁾ A hallmark of mucormycosis infection is the presence of extensive angioinvasion with resultant vessels thrombosis and tissue necrosis involving orbital blood vessels and resulting in Central retinal artery occlusion.

Herein we presented a case series of 4 patients with unilateral central retinal artery occlusion as a complication seen in post covid diabetic patients of Rhino-orbital-cerebral mucormycosis.

CASE SERIES

Case1: A 42-year-old female was admitted in emergency of LLR

hospital Kanpur UP with chief complaints of sudden loss of vision and drooping of left eyelid, difficulty in opening of mouth and pain on left side of face for last 1 month. She gave history of fever with covid 19 positive report 2 months back and history of steroid intake during her illness. She was a known case of Type 2 diabetes mellitus for last 8 years. She was well nourished, conscious, and afebrile. Vision of left eye was negative for light perception and visual acuity of right eye was 20/20. Ophthalmological examination revealed complete ptosis and total ophthalmoplegia in left eye with impairment of cranial nerve iii (oculomotor), iv (trochlear), v1 (ophthalmic division of trigeminal nerve) and vi (abducent). [Figure 1A and 1B]. Anterior segment examination showed mid dilated and fixed pupil in left eye. Fundus examination revealed a generalized retinal edema, retinal arterial attenuation, and presence of cherry red spot at the posterior pole, suggesting Central Retinal Artery Occlusion of left eye [Figure 3]. Fundoscopy of right eye was unremarkable. Her blood investigation revealed the following information [HB 11.6g/dl TLC 11000 cells/mm³, serum creatinine 1.2mg/dl, RBS 448 mg/dl HbA1C 14.3%, serum ferritin 377ng/ml]

Contrast Enhancement Magnetic Resonance Imaging report of brain and orbit [Figure 2] showed pansinusitis with ocular involvement and lesion extending into medial aspect and floor of left orbit involving medial rectus muscle and optic nerve. The lesion is involving the left orbital apex and cavernous sinus with thrombosis of internal carotid artery. The lesion extending into left buccal mucosa, retro maxillary /infra-temporal fossa, involving muscle of mastication S/o invasive fungal sinusitis with likely mucormycosis. Brain MRI suggestive of acute/sub-acute non-hemorrhagic infarct in left Parieto-occipital region. The patient underwent functional endoscopic sinus surgery with debridement of sinuses. Fungal smear of affected tissue showed thin aseptate hyphae with wide angle branching, suggestive of zygomycetes and interpretation showed mucormycosis on 10% KOH mount. Culture of biopsy specimen from sinuses showed *Rhizopus oryzae* on Sabouraud's dextrose agar. The patient was started on subcutaneous insulin and Liposomal Amphotericin B with the

monitoring of serum electrolytes and renal functions. The patient showed a dramatic clinical response with improvement in her diabetes, but her left eye remained blind with complete ptosis and complete ophthalmoplegia.



Figure 1A

Figure 1B

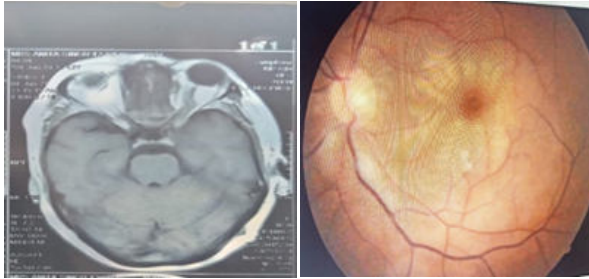


Figure 2

Figure 3

Case 2: A 40-year-old woman was admitted to emergency department LLR Hospital, Kanpur UP with chief complaints of nasal blockage on right side and loss of vision in right eye for last 1 month. She was a known case of T2DM with uncontrolled blood sugar and history of fever 2 months back with covid 19 positive report. Blood investigation revealed following information. (Plasma glucose random 468mg/dl, HBA1C 12.4%, serum alkaline phosphatase 496IU/L serum ferritin 340ng/ml). she was conscious oriented and afebrile. Visual acuity of right eye was PL negative and of left eye was grossly normal. Fundus examination revealed a generalized retinal edema, retinal arterial attenuation, and presence of cherry red spot at the posterior pole, suggesting Central Retinal Artery Occlusion of right eye. funduscopy of left eye was unremarkable. MRI scan of brain and orbit. showed pan-sinusitis with bilateral orbital involvement and thickening of optic nerve. The lesion involved right retro-maxillary region, right pterygopalatine fossa, and right muscle of mastication. There was right preseptal and buccofacial edema seen. There was deviation of nasal septum toward left side and bilateral middle and inferior turbinate hypertrophy(R>L). Aggressive surgical debridement and conservative medical management done.

Case 3: A 26-year-old male who had loss of vision in right eye with swelling of right side of face was admitted to emergency department of LLR hospital Kanpur UP. He was a known case of diabetes mellitus and had history of fever 6 weeks back with covid 19 positive report. His vision in right eye was negative for perception of light and 20/20 in left eye. Anterior segment examination revealed relative afferent pupillary defect in right eye. Ocular movement of both eyes were full in all gazes. Fundus examination revealed features of CRAO. His blood investigation revealed the following information [HB 9.1g/dl, plasma glucose random 375mg/dl, HBA1C 10.4%, serum ferritin 310ng/ml] CEMRI report showed pansinusitis with orbital involvement s/o invasive fungal sinusitis with likely mucormycosis. Brain MRI showed no obvious abnormality. Debridement of sinuses was done, and fungal staining of tissue obtained revealed thin aseptate hyphae with acute branching seen resembling zygomycetes and interpretation was mucormycosis. Subcutaneous insulin and intravenous amphotericin B were started. Patient's blood sugar got controlled but his right eye remained blind.

Case 4: A 46-year-old male came at emergency department LLR hospital Kanpur UP with chief complaints of loss of vision in his right eye with left sided nasal blockage. He gave history of fever and covid 19 positive report about 1 month back and since then several episodes of left sided nasal bleeding occurred. He was a known case of type2 diabetes mellitus and hypertension. He gave history of sudden painless loss of vision in his right following swelling and protrusion of his right eye His visual acuity in right eye was perception of light negative and in left eye 20/20. Relative afferent pupillary defect was seen in his right pupil. His ocular examination showed ocular movement full in all gazes and funduscopy of right eye showed cherry red spot at macula, attenuated vessels, and edematous retina. His blood investigation

revealed the following information [HB 9.9g/dl, platelet count 0.94 lac cell/mm³, blood urea 54mg/dl, serum creatinine 2.5mg/dl, RBS 350mg/dl, HBA1C 7.5% serum ferritin 340ng/ml].

CEMRI report PNS showed pansinusitis with right orbital involvement and lesion extending into medial aspect and roof of right orbit involving adjacent rectus muscle and optic nerve, suggestive of mucormycosis. he underwent functional endoscopy sinus surgery and debridement of sinuses done. Fungal stain and KOH mount was positive for filamentous acute angle branching fungal hyphae suggestive of Rhizopus and confirmed by biopsy. He underwent medical management with sub cutaneous insulin and intravenous Amphotericin B. His showed clinical improvement but vision loss of his right eye not reversed.

DISCUSSION

Our case series highlights the possible correlation among covid 19, diabetes and mucormycosis. Uncontrolled diabetes mellitus is a common risk factor for covid 19 infection and mucormycosis. Diabetes alters the immunologic capability of host.⁽⁴⁾ Hyperglycemic status and metabolic acidosis nourish fungal colonies by interference with neutrophilic phagocytosis and increase in serum unbound iron. Mononuclear and polymorphonuclear phagocytic cell of normal host kill Mucorales by generation of oxidative metabolites and defensins, hence neutropenic patients and those with dysfunctional phagocytosis are susceptible to develop invasive mucormycosis. In covid 19 there is profound lymphopenia and in advanced infection viral replication accentuate the inflammatory response and neutrophil and monocyte influx in blood stream.⁽⁵⁾ This leads to an imbalance between neutrophil and lymphocyte action making the patient more susceptible to systemic fungal infection. In addition administration of steroid in covid 19 patient resulted in neutrophilic leukocytosis and impaired ability of leukocytes to migrate to the site of inflammation due to inhibitory effect on cytokines and chemokines.⁽⁶⁾ It has been seen that serum iron levels are low in covid patients during disease secondary to increasing intracellular levels of iron to facilitate viral replication.⁽⁷⁾

Post covid the infected cells and macrophages undergoes ferroptosis a kind of apoptosis releasing the intracellular iron. This along with acidic PH encourages growth of Mucor which needs iron to take hold in the tissues. Mucor has 40 times more levels of iron in its walls than aspergillus and other fungi. This probably explains the high incidence of mucor in post covid patients.⁽⁸⁾ The vascular invasion of hyphae of mucor results in widespread occlusive vasculitis and thrombosis. Thus, ominous manifestations like central retinal artery occlusion, cavernous sinus thrombosis and brain infarction have been variably reported. The unfortunate eventuality of CRAO bears an incidence of 16%-20%.^(9,10) CRAO in mucormycosis is attributed to direct infiltration of a central retinal artery by angioinvasive fungal infection from the orbit.

The intracranial extension and orbital involvement may be visible on CT scan. T2- weighted MRI and contrast-enhanced T1-weighted MRI are considered superior to CT for better delineation of fungal mass. Mucosal thickening and opacification of sinuses are visualized as T2 hyperintensities on MRI.

The diagnosis is aided by recognition of typical clinical and radiological findings. A biopsy of the debrided necrotic tissue from nasopharynx, sinuses or orbit substantiates the diagnosis. KOH mount may reveal aseptate branching hyphae at right angles.

Our patients had been treated aggressively with intravenous liposomal amphotericin B and extensive surgical debridement, which remained the mainstay of treatment. The infection was controlled with an appropriate therapy, however the affected eye remained blind as visual loss due to CRAO cannot be reversed.

CONCLUSION

CRAO is a rare manifestation of rhino-orbital-cerebral mucormycosis . Post covid and poorly controlled diabetic patients with history of steroid intake and raised serum ferritin level, are prone to develop this disease. Early diagnosis, appropriate treatment of underlying disorder, aggressive surgical debridement and use of liposomal amphotericin B are key to improve outcome and reduce morbidity and mortality of this lethal infection but blindness by CRAO cannot be reversed.

Declaration of patient consent-

The author certify that they have obtained all appropriate patient consent forms. In the form the patient(s) has/have given his/her/their

consent for his/her/their images and other clinical information to be reported in the journal.

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Conflict Of Interest-nil

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