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Editorial

Indications for orbital exenteration in COVID-19 associated Rhino-orbito-cerebral Mucormycosis

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Rhino-orbito-cerebral Mucormycosis (ROCM) is an emerging, rapidly progressive life threatening opportunistic fungal infection caused by ubiquitous saprophytic fungi belonging to the class of zygomycetes, order Mucorales. It is the most common form of mucormycosis, associated with high mortality rate. The major risk factors for ROCM include immunosuppressive conditions, uncontrolled diabetes, ketoacidosis, neutropenia, renal failure, corticosteroid therapy, organ transplantation etc., Its incidence has significantly risen during COVID-19 pandemic (second wave) specially in patients with the above mentioned risk factors, moreover the inadequate lymphocyte count found in COVID-19 patients might be one of the main risk factors responsible for secondary fungal invasion.[1]

This fungi has a tendency to invade the arterial wall which leads to thrombosis consequently leading to ischemia and tissue necrosis.[2] Mucormycosis mainly originates in the nasal or oral mucosa and then spreads to paranasal sinuses and enters the orbital cavity by bony destruction or via nasolacrimal ducts, lymphatics and neurovascular bundles[3] it can lead to intracranial or cavernous sinus invasion as well which occurs either through the orbital apex or through pterygopalatine fossa.

The early diagnosis of ROCM is often difficult and challenging due to its highly variable clinical presentation.[4,5] The initial nonspecific clinical presentations are in the form of headache, fever, nasal congestion and discharge, epistaxis, mucosal necrosis and facial or dental pain. Ophthalmic manifestations gradually develop as infection spreads to the orbit. Oculo-orbital manifestations are mainly due to necrosis of cranial nerves (orbital apex syndrome), orbital cellulitis leading to orbital compartment syndrome and rarely intraocular invasion (endophthalmitis).[6,7] Ophthalmic signs and symptoms of ROCM are highly variable. Common ocular findings are pain in the eyes, conjunctival hyperemia, chemosis, periorbital swelling, ptosis, proptosis, diplopia, ophthalmoplegia and vision loss.[8,9] Sudden visual loss may be due to central retinal artery or ophthalmic artery occlusion, optic neuritis , optic nerve infarction or direct infiltration of the optic nerve, thrombosis or invasion of the cavernous sinus and rarely endophthalmitis.[6,9,10] The unilateral cranial nerve palsy (III,IV,VI nerve), signs of retinal & choroidal ischemia and optic nerve dysfunction are signs of orbital apex syndrome.

Common diagnostic tools are nasal endoscopy, contrast enhanced MRI (preferred) or CT Scan of PNS, orbit and brain. The definitive diagnosis of ROCM is based on histopathological identification of fungal structures, positive identification for Mucorales. The real-time PCR

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and DNA sequencing are commonly used molecular tools for identification of ROCM.[11] Contrast enhanced MRI is the most preferred radio-imaging for ROCM. A characteristic and early radio-imaging finding of ROCM is Black Turbinate sign (non-enhancement of nasal mucosa over turbinate on post contrast T_1W weighted image). The signs of early orbital infection are retro-orbital fat stranding and edema of extraocular muscle (best seen in saturated T_1W sequence). The lateral displacement (abscess in medial orbit) and thickening of medial rectus muscle (due to muscle infiltration) are also features of early orbital infection.[3] The optic nerve thickening and perineural enhancement with high signal intensity on diffusion -weighted imaging is indicative of optic nerve invasion. Isolated optic nerve involvement is suggestive of spread of infection through branches of ophthalmic artery and is an indication for early exenteration.[3,12] In advanced stage orbital mucormycosis radiological findings are characterized by severe proptosis and tenting of the globe (posterior globe angle <130 due to optic nerve stretching) with non-enhancement of orbital fat and muscles which suggest marked retrobulbar necrotic soft tissue (Figure 1). In T_2W MRI imaging presence of soft tissue enhancement at the orbital apex with involvement of optic canal and superior orbital fissure (SOF) are highly suggestive of the orbital apex syndrome and heterogenous soft tissue enhancement from SOF to cavernous sinus with loss of concavity of cavernous sinus are radiological findings of cavernous sinus syndrome / thrombosis.

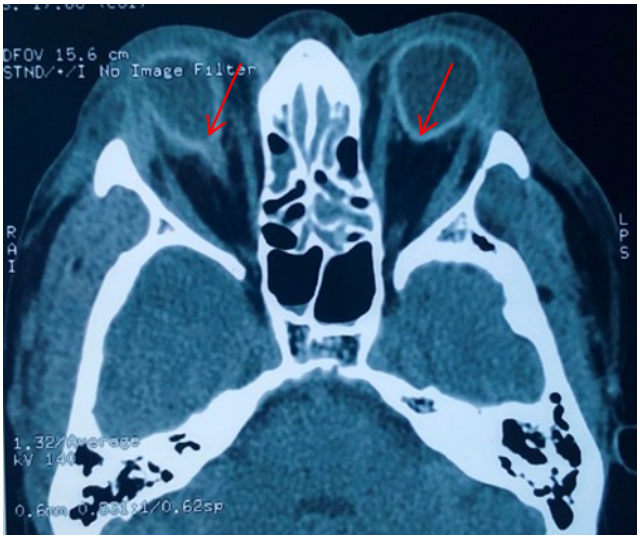

Fig. 1: CT Scan Axial view showing bilateral globe tenting.

On the basis of clinical and radiological findings orbital mucormycosis can be divided as mild or limited orbital disease and moderate to severe orbital mucormycosis. The limited orbital disease is characterized by no resistance on retropulsion of the globe, presence of extraocular movement & vision and orbital-imaging suggestive of mild disease (fat stranding or opacification in 1-2 quadrants of orbit). While features of moderate or severe disease are firm to hard consistency on retropulsion of the globe, restricted extraocular movements or frozen globe, loss of vision, ophthalmoplegia and radio-imaging suggestive of extensive orbital involvement. Honavar SG[13] proposed a staging system, on the basis of clinico-radiological findings and results of nasal endoscopy to determine the extent and severity of ROCM. It divides ROCM in 4 stages; Stage I (disease limited to nasal mucosa), Stage II (involving paranasal sinuses), Stage III (involving the orbit) and Stage IV (CNS involvement).

The treatment of ROCM requires an individualized multidisciplinary, multimodal approach including combination of appropriate systemic antifungal treatment, surgical debridement of necrotic tissues and correction of underlying conditions like hyperglycemia and acidosis etc. The poor prognostic factors in ROCM are (i) delayed diagnosis and late initiation of appropriate treatment (ii) bilateral sinus involvement (iii) cerebral involvement (iv) hemiparesis (v) facial or periocular gangrene etc.[6]

As ROCM is a rapidly progressive fatal disease, it requires early and an aggressive surgical debridement of infected & necrotic tissue of the paranasal sinuses and retro-orbital space which is recommended to obtain local control and to improve prognosis and survival rate.[14] Repeated surgical debridement may be required to remove the infected tissue. The surgical debridement not only decreases the fungal load but also improves the response of systemic antifungal treatment, as delivery of drugs to infected / necrotic tissue is hampered due to vascular tropism.

Sometime more aggressive orbital surgery such as orbital exenteration may be required to decrease fungal load and prevent direct intracranial extension.[15,16] Orbital exenteration is always associated with oculofacial disfigurement and psychological distress. Although orbital exenteration is a life saving procedure but unfortunately indications for doing exenteration remain unclear.[17] The standard guideline for orbital exenteration in treating ROCM is not available in literature.[18–20] Singh VP et al. suggested that orbital exenteration should be individualized based on retinal artery involvement, aggressiveness of the disease , underlying debilitating diseases, response of antifungal chemotherapy and visual status.[20] Levinsen et al. recommended aggressive orbital exenteration when dealing a case of ROCM with orbital apex syndrome, peribulbar or facial necrosis with or without cranial nerve involvement.[21]

In case of limited orbital disease with predominant sinonasal involvement, extensive debridement of paranasal sinuses, medial orbital compartment with or without medial wall resection with retrobulbar injection of amphotericin-B are recommended while for severe orbital disease early orbital exenteration with aggressive sino-nasal debridement

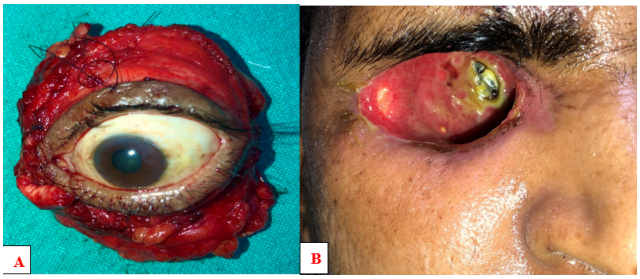

Fig. 2: (A) Specimen after orbital exenteration, (B) Photograph of post exenteration orbital socket.

has been recommended.[3,22] Shah K et al proposed "Sion hospital scoring system' to solve the dilemma associated with orbital exenteration in ROCM. The scoring system is based on three criteria; (1) clinical signs & symptom, (2) direct & indirect ophthalmoscopy and (3) radio-imaging. According to the score 1 point was given for mild symptoms/signs, 2-points for moderate symptoms/ signs and 3 points for severe symptoms & signs. According to this scoring system patients having total score ≥ 23 is said to be eligible for orbital exenteration.[23]

Hanover SG[13] proposed management algorithm for ROCM in the setting of COVID-19, according to it orbital exenteration is recommended for extensive orbital involvement (stage 3c-d; central retinal artery or ophthalmic artery occlusion, superior ophthalmic vein thrombosis, orbital apex involvement, loss of vision and bilateral involvement), limited CNS involvement (stage 4c-d; focal or diffuse cavernous sinus involvement or thrombosis) and in case of extensive CNS involvement (stage 4c-d; involvement beyond cavernous sinus, skull base involvement, brain infarction or diffuse CNS involvement) if general systemic condition of patient permits surgery.

Finally we can say that the orbital exenteration is a life saving surgical modality of treatment and should be considered for ROCM patients having severe orbital & CNS disease manifested as highly inflamed orbit with painful blind eye and frozen eye ball.

1. Conflict of Interest

None.

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