



MANAGEMENT AND FUNCTIONAL OUTCOME OF SARS COVID-19 INDUCED RHINO ORBITAL CEREBRAL MUCORMYCOSIS

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ABSTRACT

Background: Rhino-orbital cerebral mucormycosis (ROCM) is an uncommon infection caused by the angiotropic fungus belonging to the order Mucorales and has high morbidity and mortality despite treatment. Rhino-orbital cerebral mucormycosis almost always occurs in immunocompromised hosts, including patients with uncontrolled diabetes mellitus, hematologic cancers, and solid organ or hematopoietic stem cell transplants. The suspicion or diagnosis of rhino-orbital cerebral mucormycosis triggers a medical as well as surgical emergency with the delay in treatment, increasing morbidity and mortality.

Aim:

1. outcome of medical management
2. functional outcome and evaluation after medical management
3. complications of mucormycosis
4. outcome after surgical management

Methods: 62 SARS covid-19 cases were evaluated who were diagnosed with rhino orbital cerebral mucormycosis. most of the patients presented with ptosis, proptosis, orbital cellulitis, decreased visual acuity, sluggishly reacting pupils, restricted extraocular movements. some patients were known diabetics and some diagnosed with diabetes after COVID 19 recovery. Retrobulbar Liposomal Amphotericin-B (3.5mg) was given to all patients for 10 alternate days and simultaneously patients received IV LIPOSOMAL AMPHOTERCIN 300mg OD for 10 days renal function tests were monitored. **Results:** 54 of them improved on day 5 of injection most patients visual acuity improved from CF -CF to CF > 6m, patients with perception of light didn't show any improvement in visual acuity but ptosis, proptosis, conjunctival congestion and chemosis was improved and 10 patients underwent exenteration. **Conclusion:** ROCM is seen in most SARS COVID 19 who were known diabetics or post covid-19 induced uncontrolled high sugars most patients received high dose of steroids during covid 19 treatment. most patient showed improvement of symptoms after retrobulbar IV Amphotericin 3.5mg and improvement is observed on MRI stages too and some patients underwent exenteration which prevented further spread of infection.

KEYWORDS : Covid-19, rhinoorbital cerebral mucormycosis, Amphotericin-B

INTRODUCTION:

Mucormycosis is a rare and severe fungal infection [1] caused by the zygomycete, *Mucorales* [2]. These ubiquitous saprophytic fungi [3] tend to invade the wall of blood vessels, mainly the arteries, causing intima damage and, consequently, ischemia, and necrosis of the affected tissues [4]. The most common presentation is rhino-orbital-cerebral [5], evolving in 3 consecutive stages: a generally unnoticed sinus involvement, a symptomatic orbital involvement, and a cerebral involvement [1]. Paranasal sinuses are, generally, the source of the infection although it can also spread through the oral cavity or teeth [6]. The most common risk factor is diabetes mellitus, especially ketoacidosis, although other immunosuppressive conditions and renal failure are known to be predisposing conditions [7, 8].

This is a rapidly progressive and devastating condition, with survival rates of 30–70% [9]. Consequently, delayed diagnosis and treatment can be disastrous, significantly worsening the prognosis. Hemiparesis, bilateral sinus involvement, leukemia, and renal disease are also associated with lower survival rates [10]. Even in survival situations, significant morbidity and disfigurement are expected. Fungal infections are rare entities, generally associated with poor prognosis. A multidisciplinary approach between the departments of ophthalmology, otorhinolaryngology, infectious disease, endocrinology, neurology, neuroradiology, and pathology was critical to obtain the best possible outcome. Multiple factors are associated with a better prognosis, namely, early diagnosis, antifungal therapy, and aggressive debridement of necrotic and infected tissue. In this manuscript, we report such a rare case of an extensive mucormycosis infection which ultimately had a good outcome despite the delay in the diagnosis.

OBJECTIVES:

1. outcome of medical management
2. functional outcome and evaluation after medical management
3. complications of mucormycosis
4. outcome after surgical management

Case Study:.

A prospective study was done on 100 patients with rhino orbital

cerebral mucormycosis, out of which only 60 patients aged between 35-55 years (graph 1) had both orbital and sinus involvement and 2 patients had cerebral involvement.

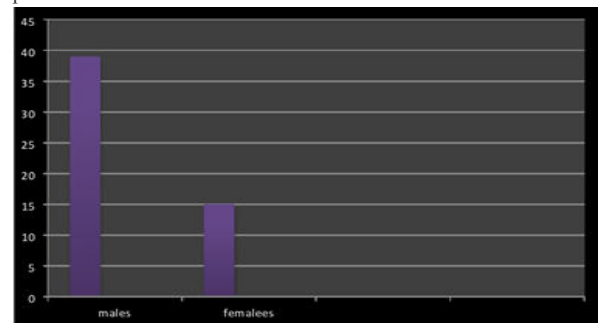


FIG (1)

All the patients initially presented with complaints of swelling of eye, drooping of eyelid, pain, blurring of vision, double vision and pain over cheeks and temple area, nasal discharge, nasal stiffness. out of 62 patients 37 patients were known diabetics under medications and rest 25 patients developed diabetes after post covid-19 who suffered moderate to severe illness of covid-19 and on IV steroids (METHYLPREDNISOLONE 40-100mg or DEXA METHOSONE 6mg bd to qid doses). 5 patients were known CKD (chronic kidney disease) on treatment. on ocular examination patients presented with decreased visual acuity (cfm to PL+ve) (table 1). with normal facial symmetry and head posture, periorbital swelling, ptosis, proptosis which is sudden onset progressive axial and unilateral in most of the cases only few presented with bilateral proptosis. Anterior segment findings showed conjunctival chemosis, congestion, exposure keratopathy and loss of corneal sensations in few cases pupils were sluggishly reacting, RAPD or mid dilated not reacting based on involvement of optic nerve fibres, lens - clear some had cataract changes. extraocular movements markedly restricted in all patients. complete ophthalmoplegia with involvement 3, 4, 6, V1, V2, cranial nerves were observed. 5 patients had involvement of only 2 muscles especially the medial rectus and lateral rectus. one

patient had primary position of gaze fixed to left side.on digital IOP finger insinuation was difficult out of 62 patients 36 had high IOP.CNS examination was done in all cases 3 cases showed decrease in power of right upper and lower limb.2cases with cerebral involvement showed loss of power,tone n sensations of limb nd patient landed up with hemiparesis and 1 patient had 2 episode of seizures.color vision and contrast sensitivity was reduced in 34 patients.

Ocular signs	males	females
Visual acuity cf>6mts to PL+	39	15
Periorbital edema	36	10
proptosis	31	9
ptosis	20	11
lagophthalmus	12	3
Conjunctival chemosis	28	9
Corneal edema	5	1
Exposure keratopathy	10	1
Anterior chamber reaction	3	nill
Pupil midilated/sluggishly reacting/not reacting to light	32	11
Lens(posterior synaechiae)	nill	nill
Extraocular movements restriction	32	10
High iop	25	7

patients were classified into stages based on MRI [table 2]and clinical correlation.all the patients had 2 or more sinuses (maxillary, ethmoid, sphenoid rarely frontal) involved.all the patients were in stage 3a to 3b.two patients were in stage 4c(fig 3,4,5).complete blood picture ,ESR,Liver function tests ,renal function tests were done.KOH mount was done in every patient from the nasal scrapings showed presence of aseptate hyphae in most of the cases and 3 cases were Aspergillus positive.biopsy tissue was taken from nasal mucosa sample and HE(haemotoxilin and eosin) histopathology showed aseptate hyphae which is considered as gold standard in diagnosing mucormycosis. constrast enhanced(Gadolinium)MRI was done in all patients showed involvement orbital Apex in 54 patients ,others had involvement of one or other recti muscles . Complications following orbitalmu cormycosis 5 pateints developed sclera abscess

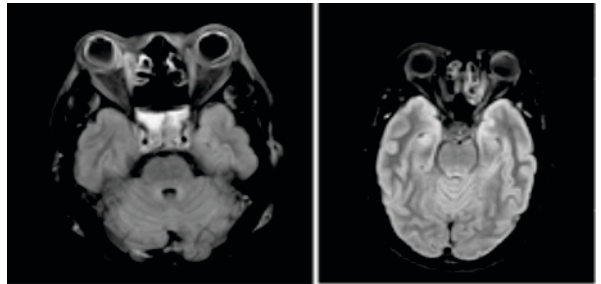


FIG(1), fistulaformation, and two amongst them developed panophthalmitis FIG(2) with intracranial extension leading acute infarcts in middle and anterior cerebral artery.11 patients developed exposure keratopathyleading to corneal melt and perforation.

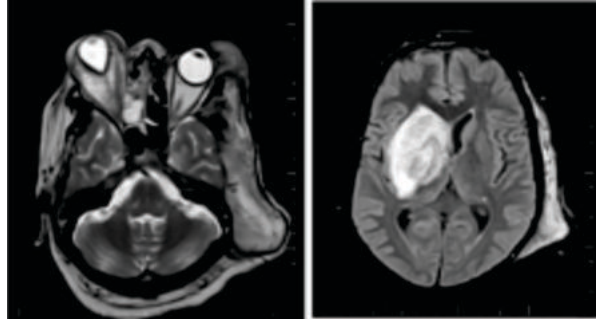
MRI



Intraconal Involvement With Involvement Of Medial Rectus, inferior Rectus Muscle



Extraconal Involvement With Involvement Of Ethmoidal Sinus Involvement



Stage Iv with Cerebral Hemisphere Involvement

Treatment:
all the patients were treated with injection IV liposomal amphotercin B 3.5mg with 1cc of 2%XYLOCAINE was in retrobulbar space on alternative days for 5 days(FIG 6,7,8) Tab.posoconazole 300mg BD stat and OD for 7days or injection posiconazole 300mg in 150ml 5% dextrose or IV liposomal amphotercin B 300mg per day for 5days.0.5%MOXIFLOXACIN eye drops 6times per day,HPMC eye drops 6times per day,0.5%TIMOLOL eyedrops 2times per day were given .systemic IV antibiotics and oral hypoglycemic drugs and INSULIN were given based on the blood sugar levels.and debridment of sinuses was done depending upon involvement stage 3b before treatment restriction of extraocular movements proptosis resolved, with improvement of eom after IV AMPHOTERCIN

RESULTS:

All the patients showed marked decrease in pain ,periorbital swelling conjunctival congestion and chemosis after retrobulbar injection Liposomal Amphotercin B out of 62 patients only 10patients showed improvement in visual acuity [fig 2] from HM to CF >5MTS and relief of ptosis ,proptosis,normal extra ocular movements with retrobulbar Liposomal AmphotercinB.out of 62 patients 18 patients were SARS COVID-19 positive who received DEXAMETHASONE 6mg BD for

Proposed Staging of Rhino-Orbito-Cerebral Mucormycosis (ROCM)

Staging of Rhino-Orbito-Cerebral Mucormycosis	Symptoms	Signs	Primary Assessment	Confirmation of Diagnosis
Stage 1: Involvement of the nasal mucosa 1a: Limited to the middle turbinate 1b: Involvement of the inferior turbinate or ostium of the nasolacrimal duct 1c: Involvement of the nasal septum 1d: Bilateral nasal mucosal involvement	Nasal stuffiness, nasal discharge, foul smell, epistaxis	Foul-smelling sticky mucoid or black-finged, or granular or haemorrhagic nasal discharge, nasal mucosal inflammation, erythema, violaceous or blue discoloration, pale ulcer, anaesthesia, ischaemia, eschar	Diagnostic nasal endoscopy. Contrast-enhanced MRI (preferred) or CT-scan	Deep nasal swab or endoscopy-guided nasal swab or nasal mucosal biopsy for direct microscopy, culture and molecular diagnostics; nasal mucosal biopsy for rapid histopathology with special stains
Stage 2: Involvement of paranasal sinuses 2a: One sinus 2b: Two ipsilateral sinuses 2c: Two ipsilateral sinuses and/or palatine cavity 2d: Bilateral paranasal sinus involvement or involvement of the zygoma or mandible	Symptoms in Stage 1 + facial pain, facial edema, dental pain, systemic symptoms (malaise, fever)	Signs in Stage 1 + unilateral or bilateral, localized or diffuse facial edema, edema localized over the sinuses, localized sinus tenderness	Diagnostic nasal endoscopy. Contrast-enhanced MRI (preferred) or CT-scan	Same as Stage 1 + sinus biopsy for direct microscopy, culture and molecular diagnostics and rapid histopathology
Stage 3: Involvement of the orbit 3a: Nasolacrimal duct, medial orbit, vision unaffected 3b: Diffuse orbital involvement (>1 quadrant or >2 structures), vision unaffected 3c: Central retinal artery or ophthalmic artery occlusion or superior ophthalmic vein thrombosis, involvement of the superior orbital fissure, inferior orbital fissure, orbital apex, loss of vision 3d: Bilateral orbital involvement	Symptoms in Stage 1 and 2 + pain in the eye, proptosis, ptosis, diplopia, loss of vision, infraorbital and facial V1 V2 nerve anaesthesia	Signs in Stage 1 and 2 + conjunctival chemosis, isolated ocular motility restriction, ptosis, proptosis, infraorbital nerve anaesthesia, central retinal artery occlusion, features of ophthalmic artery occlusion and superior ophthalmic vein thrombosis, V1 and V2 nerve anaesthesia, and features of II, IV and V1 nerve palsy indicating orbital apex/superior orbital fissure involvement	Diagnostic nasal endoscopy. Contrast-enhanced MRI (preferred) or CT-scan	Same as Stage 2 + orbital biopsy if indicated and if feasible (if the disease is predominantly orbital) for direct microscopy, culture and molecular diagnostics and rapid histopathology
Stage 4: Involvement of the CNS 4a: Focal or partial cavernous sinus involvement and/or involvement of the cribriform plate 4b: Diffuse cavernous sinus involvement and/or cavernous sinus thrombosis 4c: Involvement beyond the cavernous sinus, involvement of the skull base, internal carotid artery occlusion, brain infarction 4d: Multifocal or diffuse CNS disease	Symptoms in Stage 1 to 3 + bilateral proptosis, paralysis, altered consciousness, focal seizures	Signs in Stage 1-3 (some features overlap with Stage 3) + V1 and V2 nerve anaesthesia, ptosis, and features of II, IV and V1 nerve palsy indicate cavernous sinus involvement. Bilaterality of these signs with contralateral orbital edema with no clinico-radiological evidence of paranasal sinus or orbital involvement on the contralateral side indicate cavernous sinus thrombosis. Hemiparesis, altered consciousness and focal seizures indicate brain invasion and infarction.	Diagnostic endoscopy. Contrast-enhanced MRI Scan, MRI (preferred)	Same as Stage 3

5 days showed no improvement. 34 patients who were post COVID 19 showed no improvement in visual acuity, proptosis except relief of conjunctival congestion, chemosis and pain. All these patients were planned for exenteration (fig 9,10,11). out of 34 patients 5 undergone exenteration till now, out of 62 patients only 5 showed positive for urine ketone bodies and rest were suspected due to poor metabolic control.



Stage 1Va



Lid Sparing Exenteration Surgery



After Exenteration Surgery

DISCUSSION:

mucormycosis occurring in a diabetic patient with poor metabolic control and in diabetic ketoacidosis. Acidosis disrupts the iron-binding of transferrin, increasing the amount of unbound iron and promoting fungus growth [1]. Also, the polymorphonuclear dysfunction in diabetic patients, characterized by a delayed margination, encourages fungal proliferation [11]. Additionally, diabetic bronchoalveolar macrophages present a diminished ability to

inhibit spore germination [12]. Generally, infection is acquired by inhalation of spores. Here, though, it was presumed to start in the long-standing teeth infection, with subsequent spread into the paranasal sinus and then orbital structures.

Mucormycosis is characterized by vascular tropism because spores and germ tubes adhere to and damage endothelial cells [13]. This phenomenon may lead to ischemic necrosis of host tissues, namely the orbital walls, ocular nerves, and the ophthalmic artery. Ophthalmic signs and symptoms of this disease are variable, with ophthalmoplegia, vision impairment, and proptosis being the most common [14]. Other symptoms include periorbital pain and chemosis [2]. Several other nonophthalmic signs include sinusitis, nasal discharge, facial swelling, cranial nerve VII palsy, and palatal necrosis. In this case, the simultaneous dysfunction of the optic nerve and the cranial nerves III, IV, VI, V1, and V2, along with signs of retinal and choroidal ischemia seen in funduscopy, were highly suggestive of an orbital apex syndrome with unilateral involvement. This entity is a well-recognized presentation of mucormycosis, but other etiologies could also be considered. The definitive diagnosis was based on histopathological identification of fungal structures and positive culture for *Mucorales*. Typically, large nonseptate mycelial filaments branching at a right angle are visible [1]. However, the rates of successful tissue cultures are only 33–50% [15] probably because of hyphae damaging during manipulation, suboptimal standard culture conditions, and prolonged antifungal pretreatment [16, 17]. This low rate of positive cultures for mucormycosis could lead to misleading conclusions and consequently delay the diagnosis. During the acute phase, several surgeries were necessary to improve the general condition and provide a diagnosis. This situation led to a delay in the diagnosis. Although already reported [6, 18], polymicrobial cultures are uncommon. So, despite the variety of pathogens identified in the mycobacteriological study, we considered *Mucorales* the causal agent in the presenting case. Accordingly, adequate antifungal therapy was provided based on that assumption.

Treatment of *Mucormycosis* requires a multidisciplinary approach. Major risk factors, such as ketoacidosis or hyperglycemia, must be controlled. Although the delivery of the drugs to the necrotic tissue may not be an easy task, medical treatment with systemic antifungal agents is essential, with reported survival rates of 72% [1]. However, due to vascular tropism, it may be difficult to deliver the drugs to the necrotic tissue. Liposomal amphotericin B is the first choice of treatment, but it requires careful monitoring due to its renal toxicity. Posaconazole is another effective drug [2].

Early and aggressive debridement of necrotic or infected tissue is of critical importance. In this case, the multiple surgical interventions to remove the infected tissues could have contributed to the survival of the patient, even though no fungal agent was identified. A more invasive strategy, such as surgical exenteration could also be necessary to diminish fungal load and avoid direct cerebral extension [2]. Given the lack of response to previous treatment modalities, it was the way to stop the progression of the infection. Other treatment options, such as the hyperbaric chamber, are advocated in an attempt to provide oxygen flow to ischemic tissues, therefore, improving neutrophil activity and promoting wound healing [20].

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