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REVIEW ARTICLE

Orbital mucormycosis in COVID-19: An overview

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Abstract

Rhino-orbital cerebral mucormycosis is an aggressive and a rapidly progressive fungal infection that can affect the paranasal sinuses, orbit and brain.The aim of this review article is to discuss the etio-pathogenesis, clinical course and management options of this highly destructive fungal infection.

Introduction

Rhino-orbital cerebral mucormycosis (ROCM) is an opportunistic, highly aggressive, and potentially fatal infection. It usually affects patients with uncontrolled diabetes, hematological malignancies, neutropenia, solid organ transplants, and patients on chemotherapy or desferrioxamine.[1,2] The overall incidence of ROCM in diabetics in the pre-Coronavirus disease (COVID) era was reported to be 0.15%.[3]

In, recent times a sudden surge in the cases of ROCM has been noted in India, with the disease being declared an epidemic in Tamil Nadu, Odisha, Gujarat, Rajasthan, Telangana, and Chandigarh.[4]

Etiopathogenesis

Orbital mucormycosis is caused by the subset of Zygomycosis, order Mucorales which includes *Mucor*, Rhizopus, and Absida [Figure 1]. The most common reported causative agent of ROCM is *Rhizopus oryzae* followed by *Mucor* sp.[5]

The fungal spores are present freely in the environment and enter through the nasal mucosa. In immunocompetent individuals, the fungal spores are phagocytosed by the macrophages and polymorphs and are killed by the oxidative stress caused due to generation of free radicals. This prevents the further spread of infection. However, in immunocompromised patients, there is an impairment of chemotaxis and phagocytosis by macrophages and polymorphs. Acidic pH and an increase in the levels of free iron in patients with diabetic ketoacidosis promote survival of the fungal spores. Mucormycosis is characterised by extensive angioinvasion which results in thrombosis and rapid tissue necrosis. Angioinvasion also promotes the hematogenous spread of infection to noncontiguous sites.[6]

COVID-19 and Mucormycosis

Severe acute respiratory syndrome (SARS COV-2) is a novel enveloped virus known to cause harmful respiratory infections in humans, which emerged in December 2019. A large number of studies have found an increased risk of SARS-COV2 viral infection in patients with comorbidities such as diabetes mellitus, hypertension, and obesity.[7-9]

Song *et al*., based on a retrospective analysis in the Chinese population, raised the suspicion of an increased risk of invasive fungal infections in patients recovered/recovering from COVID infection.[10] An increase in the ROCM cases was subsequently also reported by many authors from India during the 2nd wave of

COVID-19 infection. This association of ROCM in active Covid or Covid recovered cases has partly been hypothesised to be due to an impaired neutrophil and phagocyte function caused by the Covid infection itself resulting in an immune-compromised state. In addition, the SARS-COV-2 virus enters the cells through ACE 2 receptors, which are expressed in a large number of organs, such as lungs, kidneys, and pancreas. This may result in damage to the insulin-secreting pancreatic cells leading to new-onset diabetes.[11] Thus, COVID infection not only induces an immunocompromised state in the patient but also increases the risk of new-onset diabetes or uncontrolled sugars in an already diagnosed case of diabetes mellitus.

Furthermore, lifestyle changes and restriction of outdoor visits and activities in the Covid times may result in an increased risk of various metabolic syndromes in previously healthy individuals;[12-15] and an increased risk of uncontrolled blood sugar in already known diabetics further increasing the proportion of the population at risk of developing mucormycosis.

Recently, 5 case series have been reported on Covid associated mucormycosis. The salient features of these studies are summarized in Table 1.[16-20]

Clinical Presentation

The initial symptoms of Rhino orbital mucormycosis include facial or periocular pain, nasal stuffiness, nasal crusting, and/or foul-smelling nasal discharge.

Ophthalmic signs may include conjunctival congestion, chemosis, proptosis, ptosis, complete ophthalmoplegia, and vision loss [Figure 1a and 2a]. Vision loss can be either due to perineuritis or due to ophthalmic artery occlusion, and central retinal artery occlusion.[21,22] Due to the angioinvasive nature of the fungus, there is extensive necrosis of orbital and periorbital tissues. Eyelid skin may appear to be dark-colored, dry and atrophic due to loss of blood supply. The presence of black eschar indicates necrosis of tissues, especially in the nasopharynx and oropharynx. The presence of black eschar is pathognomonic of mucormycosis in patients with uncontrolled diabetes and in immunocompromised conditions. The involvement of the inferotemporal fossa may result in difficulty in chewing, seventh nerve palsy, temporal fossa fullness and difficulty in mouth opening. Cavernous sinus involvement can result in bilateral chemosis, proptosis, ophthalmoplegia, and loss of sensation along with the distribution of ophthalmic (V1) and maxillary (V2) division of trigeminal nerve. Abduction limitation in the contralateral eye due to a 6th nerve involvement is one of the first signs of cavernous sinus involvement. The infection from the cavernous sinus can spread to the temporal and occipital lobes further deteriorating the patient's general condition, leading to disorientation.

Diagnosis

Imaging

Magnetic resonance imaging (MRI) with contrast demonstrates variable T1 and T2 signal intensities in paranasal sinuses (PNS) with devitalized mucosa appearing as contiguous foci of nonenhancing tissue, seen as a black turbinate sign. T1 phase of MRI shows lesions that are isointense to brain parenchyma. Lesions show variable intensity on T2 phase with around 20% of patients showing hyperintense signals [Figure 2c] while fungal elements themselves tend to have a hypointense signal on T2.[23]

Table 1: Literature review of the case series on Orbital Mucormycosis and COVID-19

Author/Year	Age	Associated comorbidities	Intervention done	Explaination
Sen/2021 *n* = 6	46.2–73.9 years	Diabetes *n* = 6 Hypertension *n* = 3 CAD, *n* = 1 COVID-19 *n* = 6	Exenteration, *n* = 2	Poorly controlled diabetes with use of steroids
Sarkar/2021 *n* = 10	23–67 years	Diabetic ketoacidosis at presentation, *n* = 4 Covid-19, *n* = 10	Exenteration, *n* = 1 Maxillectomy, *n* = 3 Death within 1 month, *n* = 4	COVID-19 has a predisposition for extensive pulmonary involvement, and by itself predisposes to invasive fungal infections
Moorthy/2021 *n* = 18	35–73 Years	Diabetes, *n* = 16 COVID-19, *n* = 18	Exenteration, *n* = 7 Death, *n* = 6 Lost to follow-up, *n* = 1	Steroid use in COVID-19
Sharma/2021 *n* = 23 Orbit involvement in *n* = 10	--	Diabetes, *n* = 21 COVID-19, *n* = 23	Exenteration, *n* = 0 (patients had good visual acuity and ophthalmic examination details not available)	Extensive steroid and broad-spectrum antibiotic use for Covid-19 management
Ravani/2021 *n*=31	56.3 years	Diabetes, *n*=30 COVID, *n*=19 IVMP, *n*=19	Exenteration, *n*=4/31 Death=3	Uncontrolled diabetes Poor dietary control and medical care during lock-down phase

Cavernous sinus thrombosis presents as irregularity and narrowing of ICA.

A contrast-enhanced computed tomography (CECT) scan may not show any significant findings in early cases and in such cases, CE MRI must be performed. CECT can show a lack of enhancement in the cavernous sinus area in cases of thrombosis. PNS may show fluid levels or opacification and bone destruction. However, these findings are nonspecific. Ethmoid sinuses are involved most commonly, and invasion through the medial wall of orbit can be well appreciated. However, sometimes, the spread of infection can also take place from the floor, through the inferior-orbital foramen.[24]

Microscopic diagnosis-potassium hydroxide staining (KOH staining)

KOH staining of deep scrapings and biopsies of involved tissue appearing as black eschar in the paranasal sinus or nasal cavity should be done as an emergency procedure. Nasal swabs yield fungal elements in only around 25% of cases and thus can be misleading. Deep nasal biopsies are more reliable and must be preferred. The fungal invasion may be patchy, so multiple biopsies may be required. The presence of broad, irregular, ribbon-like, non-septate, and right-angled branching hyphae is suggestive of mucormycosis. KOH calcofluor stain can help to better appreciate the fungal elements.[25] Histological examination of biopsy tissue shows characteristic angioinvasion and tissue infarction. Fungal hyphae can also be demonstrated with Grocott-Gomori methenamine–silver nitrate, periodic acid–Schiff, or calcofluor white stain. On the Grocott Gormori stain, fungal elements appear black on the green background. Sabouraud dextrose agar culture helps in the characterisation of fungal species.

Systemic investigations

Systemic workup including complete blood counts to rule out neutropenia, random blood sugar, hemoglobin A1c, and urine ketones, to rule out keta-acidosis and a baseline electrocardiogram (ECG), serum electrolytes and renal function test must be done.

Treatment

Management of orbital mucormycosis is an emergency and requires a multidisciplinary approach including an endocrinologist, ophthalmologist, neurosurgeon, ocular microbiologist, otolaryngologist, and a physician. The management is essentially three-pronged and requires urgent correction of the metabolic derangement/immunosuppression, followed by initiation of systemic amphotericin B (AMB) and prompt debridement of the necrotic tissue. A delay in treatment can significantly worsen the prognosis.[26]

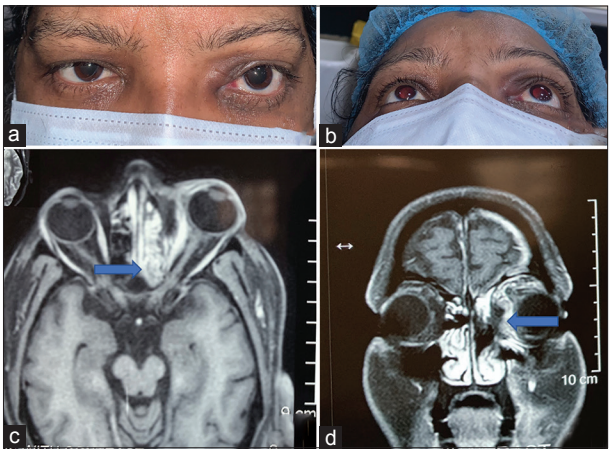

Figure 1: (a and b) Clinical picture of a patient showing left upper eyelid edema, with mild lateral dystopia and (1b) mild proptosis on worm's eye view. (c and d) Contrast -enhanced magnetic resonance imaging of orbit (axial and coronal cuts) showing pansinusitis and erosion of left medial orbital wall with enhancing lesion along medial orbital wall and thickening and enhancement of medial rectus muscle

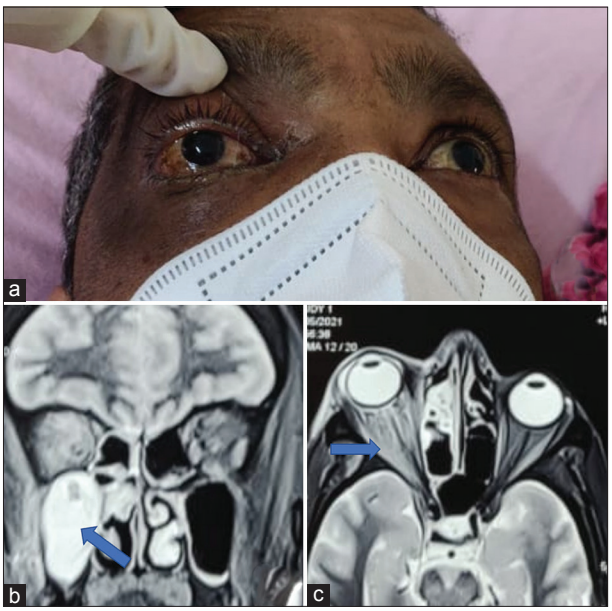

Figure 2: (a) Clinical picture of the patient showing right eye conjunctival chemosis with proptosis, complete ptosis, and darkening of periocular skin. (b) Contrast-enhanced magnetic resonance imaging (MRI) of orbit (coronal cuts), showing pan-sinusitis with the extension into soft tissue of posterior masticator space. (c) T2 weighted MRI of orbit (axial cuts), showing right axial proptosis, with ethmoid sinusitis and hyperintensity of the retrobulbar intraconal space

Antifungal therapy

AMB

AMB is the drug of choice for the treatment of mucormycosis.[27]

AMB is a fungicidal drug and acts by increasing the permeability of the fungal cell membrane. Lipid formulations of AmB are significantly less nephrotoxic as compared to conventional deoxycholate AMB and can be safely administered at higher doses for a longer period.

A number of case studies have demonstrated liposomal AMB to be a better option.[28] After sensitivity testing, liposomal AMB is administered intravenously in the dose of 5 mg/kg/day,

in 5% dextrose for 4–6 weeks.[29] There are no clear guidelines on the cumulative dose of AMB and it needs to be tailored to each patient, depending on the renal functions, and clinical and radiological resolution of the disease. The side effects of AMB include nephrotoxicity, electrolyte imbalance, hepatotoxicity, anaemia, infusion-related acute reaction and central nervous system toxicity. Hence, it is essential to do regular monitoring of renal function test, serum electrolytes and ECG in a patient receiving AMB.

Posaconazole

Posaconazole is a fungistatic drug that acts by inhibiting the ergosterol production by binding and inhibiting the lanosterol-14α-demethylase.[30]

Posaconazole is available in oral suspension, a delayed-release tablet, and intravenous formulations. Once the course of intravenous AMB is completed, the patients are started on an overlapping dose of oral posaconazole for 4–7 days, till the trough serum levels of posaconazole reach >0.7 ug/ml. The patients are then shifted to oral Posaconazole. The dose of oral Posaconazole is 300 mg twice a day for 1 day, followed by once a day which is continued to 6–12 months.[31] Intravenous Posaconazole may be used in patients not tolerating or allergic to AMB. It is administered through a slow infusion route over 90 min in a dose of 300 mg BD for the first 2 days.[32]

Adverse effects of posaconazole are diarrhoea, nausea and vomiting, hypokalemia thrombocytopenia, heptao-toxicity and rarely haemolytic uremic syndrome, pulmonary embolus, adrenal insufficiency, TTP, and hypersensitivity reaction.

Isavuconazole

Isavuconazole is a novel triazole with the mechanism of action being similar to voriconazole. The drug has a broad spectrum of action encompassing a wider range of fungal species, including Mucorales and is efficacious as primary therapy in patients infected with rare fungi. Isavuconazole is administered at a dose of 200 mg oral/intravenously 8 hourly for 6 doses followed by a maintenance dose of 200 mg orally or intravenously once a day, beginning within 12–24 h after the last loading dose.[33]

Retrobulbar AMB

Retro-orbital injections of AMB have been tried in patients as an adjunct to systemic antifungal drugs and sinus debridement. This form of direct drug delivery has the potential to overcome limited penetration of the systemically administered antifungal drugs into the necrotic tissues of the orbit. Orbital injections of AMB have been tried occasionally in patients with invasive orbital aspergillosis as a minimally invasive globe sparing option.[34-36]

In a case report of rhino-orbital mucormycosis, Hirabayashi *et al.* injected 1 ml of 3.5 mg/ml deoxycholate AMB with an antecedent retrobulbar injection of anaesthetic (2% lidocaine and 0.5% mar- caine in a 1:1 ratio) delivered to the right medial intraconal space daily for 3 days.[37] The patient also underwent adjuvant sinus debridement. A reduction in the visual acuity was noted on day 15 which was attributed to the progression of the disease rather than toxicity of AMB, and in the final follow-up, the patient had a visual acuity of 20/20.

Luna *et al.* in another case report avoided exenteration by intraconal AMB injections.[38]

Hyperbaric oxygen

Hyperbaric oxygen can also be used as an adjunct to AMB. Hyperbaric oxygen acts by increasing oxygenation, decreasing acidosis, and increasing phagocytic activity.[39]

Surgical Management

Surgical debridement is required in the treatment of mucormycosis as the antifungal drugs cannot penetrate the dead necrotic tissues. Depending on the extent of bony necrosis, maxillectomy or ethmoidectomy may be required.

Orbital exenteration may be required when orbital tissue is involved. There are no universal guidelines on when to perform orbital exenteration. The decision is based on the extent of involvement of orbital tissues, the vision of the affected eye, the likelihood of further spread of infection and the general condition of the patient. Severe proptosis with a strongly positive retropulsion and no vision in the involved eye is a clear indication for exenteration [Figure 2]. However, it is in the cases with mild proptosis and limited orbital involvement where ophthalmologist face a dilemma regarding the decision to exenterate [Figure 1].[40]

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