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Case Study

Rhino Orbital Mucor Mycosis in Corona Virus Disease Pandemic: A Challenge

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Abstract

Mucor mycosis or phycomycosis is the fungus which invades the nasal cavity, and then spreads to mucosa of the paranasal sinuses and further invade orbital spaces and brain through orbital apex. The sudden emergence of high-volume cases of this entity are seen in the setting of Corona Virus Disease-19 (COVID-19) in India which has raised the global alarm. It is opportunistic infection predisposed by diabetes mellitus, corticosteroids, immunosuppressive drugs and immune-compromised patients. Various clinical presentations such as headache, nasal congestion, nasal ulcers or nasal discharge, epistaxis, toothache, fever or malaise have been witnessed. Presenting symptoms include facial or periorbital swelling or numbness, proptosis, ptosis, chemosis, diplopia, ophthalmoplegia, corneal anaesthesia and loss of vision. Rhino orbital cerebral Mucor mycosis (ROCM) can be categorized as Possible, Probable, and Proven. Optimal medical therapy relies on correction of underlying systemic abnormalities, such as acidemia and hyperglycaemia, along with prompt antifungal medical therapy and aggressive surgical intervention. Early aggressive surgical debridement is of paramount importance for this infection. The goal is to remove all necrotic tissue done endoscopically or through an open approach till the involved tissues bleed.

Keywords: *Corona Virus Disease-19; Rhino Orbital Cerebral Mucor Mycosis; Central Retinal Artery Occlusion; Septate Hyphae; Transcutaneous Retrobulbar Amphotericin B*

Introduction

Mucor mycosis is also known as phycomycosis and zygomycosis. It is an aggressive opportunistic fungal infection and is caused by organisms of the family Mucoraceae (including the genera *Mucor, Absidia*, and *Rhizopus*) [1].

This fungus is ubiquitous in nature and is found in soil and on decaying vegetation. This infection is seen in immunocompromised status as macrophages ingests the spores, but in immuno-compromised status, these spores get germinated and develop infection in sinuses and lungs. The fungus invades the nasal cavity, and then spreads to mucosa of the paranasal sinuses which further shows its spread to the orbital spaces and apex. This infection further propagates its access to the brain via the orbital apex or the optic nerve sheaths. This spread is also known as Rhino orbital cerebral Mucor mycosis (ROCM). The presentation of this pathology is usually with non-specific symptoms and then it shows typically a rapidly progressive infection associated with a high mortality rate. The sudden exponential increase in the ROCM cases in the setting of COVID-19 in India has raised the global alarm against this fatal infection [2].

Risk factors

Mucor mycosis is potentially lethal fungal infection. It is opportunistic infection predisposed by diabetes mellitus, corticosteroids, immunosuppressive drugs, immune-compromised patients with severe neutropenia immunodeficiency, malignancies (solid organ, haematological) and iron overload [3].

Pathogenesis

The organisms being Angio invasive in nature, the fungal hyphae invade the blood vessels leading to infarction, necrosis and bone destruction [4].

These organisms are ubiquitous and air-borne, frequently found in bread mould, soil, manure, and decaying vegetation. The spores gain entry via inhalation to the nasal and oral mucosa and proliferate and geminate into hyphae. From the mucosae, the spores/hyphae invade the paranasal sinuses especially ethmoid sinus and shows its invasion through the thin lamina papyracea and gain access to the orbit and its contents. The organism thrives in this matrix of dead organic tissue and continues to spread by direct extension along injured blood vessels. Orbital extension can also occur via the nasolacrimal duct leading to orbital apex syndrome which results in vision loss due to involvement of the optic nerve or by arterial infarction as central retinal artery occlusion. Superior orbital fissure and its contents, such as cranial nerves III, IV, and VI, and branches of V1 and V2 also gets involved and may cause diplopia, proptosis and total ophthalmoplegia. It further shows its extension to the cavernous sinus and brain parenchyma, causing vascular thrombosis and infarction.

Clinical features

The clinical presentation can be non-specific such as headache, nasal congestion, nasal ulcers or nasal discharge, epistaxis, toothache, fever or malaise. The infection can further penetrate the sinuses and thick black necrotic tissue known as eschar are seen on the inferior turbinates' and hard palate which is characteristic of maxillary sinus involvement. This infection can further invade the ethmoid bone by angioinvasion and can enter the orbit. Various symptoms include facial or periorbital swelling or numbness, proptosis, ptosis, chemosis, diplopia, ophthalmoplegia and corneal anaesthesia (Figure 1). The loss of vision can happen due to invasion of the orbital nerves and vessels such as central retinal artery occlusion [Figure 2].

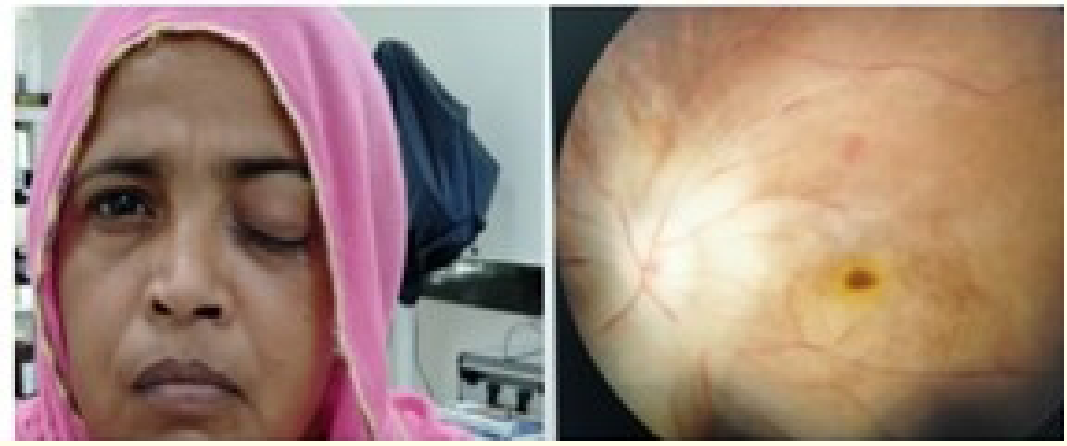

Figure 1 and 2: *Showing left eye ptosis, proptosis and central retinal artery occlusion on fundus examination.*

The cavernous sinus thrombosis with vision loss can also be the presentation. The other presentations can be hemiparesis, or seizures suggests intracranial invasion which takes place through ophthalmic artery, superior orbital fissure via internal carotid artery occlusion, cribriform plate via perivascular and perineural sheaths or orbital apex [5]. The course of the disease can be very short and late symptoms and signs indicates a poor prognosis.

Various diagnostic categories of ROCM

ROCM can be categorized as possible, probable and proven.

Any patient having signs and symptoms of ROCM in concurrent or recently (< 6 weeks) treated COVID 19 with any of the risk factors is considered as possible ROCM. When the clinical symptoms and signs are supported by diagnostic nasal endoscopy findings along with the imaging modalities such as contrast-enhanced MRI or CT scan is considered as Probable ROCM. Proven ROCM is when clinico-radiological features coupled with microbiological confirmation on direct microscopy or culture or histopathology with special stains or molecular diagnostics are essential to categorize a patient as Proven ROCM [7].

Staging of ROCM [7]

Stage 1	Stage 2	Stage 3	Stage 4
Stage 1: Nasal mucosa and sinuses 1a: Middle turbinate 1b: Inf. Turbinate 1c: Nasal Septum 1d: Bilateral nasal mucosa (deep swab, endoscopic mucosal biopsy)	Stage 2: Paranasal sinuses involvement 2a: One Sinus, 2b: Two Sinuses, 2c: > Two Sinuses, 2d: Bilateral sinuses, with zygoma or mandible	Orbital involvement 3a: Naso lacrimal duct 3b: Diffuse orbit, vision not involved 3C: Central retinal artery occlusion, Superior orbital fissure, inferior orbital fissure, Optic nerve 3d: Bilateral orbit	4a: Focal cavernous sinus involvement 4b: Diffuse cavernous sinus 4C: Beyond cavernous sinus, Skull base, Internal carotid artery occlusion, brain infarct, 4d: Multifocal central nervous system disease

Diagnostic modalities

Biopsy

Direct scrapings, biopsies or fluids of involved tissue nasal mucosa, nasal septum or paranasal sinuses are diagnostic. These locations can be involved in patchy manner. If one biopsy gets negative results, repeated biopsies can be sent again.

Endoscopic debridement

It can be done and the biopsy obtained can also be sent. Identification of non-septate, right-angled branching hyphae are seen on potassium hydroxide mount and calcofluor white staining is also a tool for rapid diagnosis and necrotic tissue is most suitable for this. Various stains such as Grocott-Gomori methenamine-silver nitrate, periodic acid-Schiff, or calcofluor white can be used for this histopathological purpose. Angioinvasion and tissue infarction can be seen on histopathology. Mucorales organisms are seen as invading connective tissue adjacent to areas of necrosis. Typical hyphae seen are broad with irregular, thin, nonparallel cell walls lacking septae.

Culture

Culture can be done to test for a phycomycotic infection and tissue fragments or swabs should not be considered negative for at least two weeks. Brain heart infusion broth, potato dextrose agar and Sabouraud's dextrose agar with gentamicin and polymyxin-B can be used for this purpose.

Radiological imaging

ROCM can be diagnosed both by Computed tomogram (CT) and magnetic resonance imaging (MRI). MRI is ideal for delineating the anatomical spread of the infection in order to manage this. MRI helps in localisation of the blood vessels infiltration, soft tissue involvement, mucosal thickening, intracranial extension, orbital cellulitis and orbital fat and lids infiltration with the infection (Figure 3).

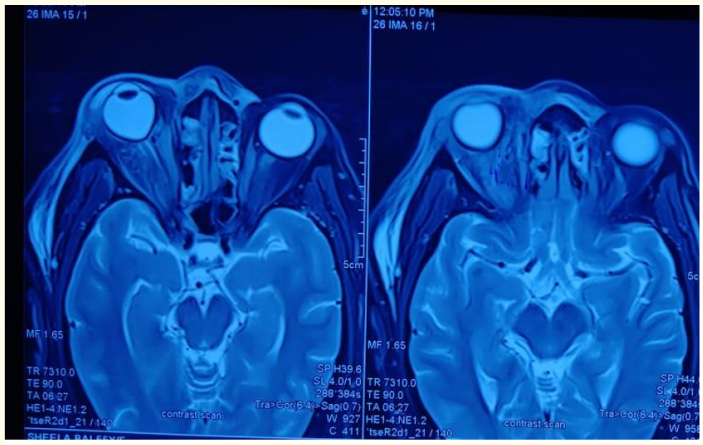

Figure 3: *MRI orbit showing T2 signal enhanced hyperintense images of extraocular muscles, retro and peri orbital fat, optic nerve sheaths showing post contrast heterogenous enhancement.*

CT shows soft tissue thickness along the paranasal sinuses, opacification of the sinuses. It also shows fluid levels in the sinuses, bone destruction, erosion or surrounding necrosis. On MRI with T1 and T2 intensity shows focal devitalized mucosa without any enhancement. Contrast-enhanced CT(CECT) scans may show lack of enhancement in the region of cavernous sinus which is consistent with thrombosis from the invasive fungus.

Diagnosis based treatment

Strict metabolic correction of acidaemia and hyperglycaemia with antifungal medication and aggressive surgical intervention is mandatory for this aggressive and lethal infection.

Possible ROCM	Probable ROCM	Proven ROCM
Supportive treatment is given along with repeat diagnostic biopsy after 24 hours and CECT and MRI after 72 hours. If the condition of the patient improves on supportive treatment and the imaging shows nothing specific, observe the patient after 3 months.	Induction therapy of the patient with liposomal amphotericin B 5 - 10 mg/Kg with strict metabolic control. Other alternative is amphotericin B deoxycholate and Amphotericin B Lipid complex which are more toxic and less effective but economical. If the renal function tests of the patients are deranged then Isavuconazole, 200 mg thrice a day Intravenous on day 1 - 2, followed by 200 mg once a day from day 3, I/V Posaconazole 300 mg twice daily followed by 300 mg once daily. Surgery can be planned accordingly	Treatment started same as for probable ROCM and then staging is done and further management depends upon the staging of the disease.

Medical treatment

As soon as the diagnosis is suspected the medical treatment along with the glycaemic or metabolic control, intravenous therapy with Amphotericin B should be started.

It destroys the cell wall of the fungus, is the first-line medical treatment for Mucor mycosis. As this drug is nephrotoxic and high doses are required, in that case liposomal formulations are preferred spite being given in high doses can protect the renal function.

Posaconazole, a triazole that inhibits growth of the fungus can be used as an alternative or adjunctive therapy, but not as first line therapy.

As basic pathology remains as angioinvasion and vessels are occluded, the medication often is unable to reach the affected tissue and ultimate resort is surgical intervention.

Surgical treatment

Early aggressive surgical debridement is of utmost importance done either endoscopically or through an open approach. The goal of the surgery is to remove all necrotic tissue and to encounter bleeding of the tissue as this tissue rarely bleed. Repeated debridement can be done to remove the necrotic tissue. With extensive spread of the disease, orbital exenteration, along with removal of the sinuses, may be necessary.

In cases of proven ROCM, the management is done on the basis of the staging which is as follows.

Stage 1-2,3 a,b	Predominantly sino nasal involvement is there with no or minimal orbital involvement. Visual acuity is usually spared.	Debridement of the paranasal sinuses (turbinectomy, palatal resection, medial orbital wall resection) by the surgical approach. In case of the orbital involvement transcutaneous retrobulbar amphotericin B (TRAMB) 3.5 mg/ml should be given
Stage 3 a-c	If the orbital disease progress with in ≤72 hrs.	Orbital exenteration
Stage 3 c-d	Limited to orbit	Orbital exenteration
Stage 4a	CNS involvement	Orbital exenteration and Debridement of the paranasal sinuses (turbinectomy, palatal resection, medial orbital wall resection) by the surgical approach with.
Stage 4a-c	Extensive CNS involvement	If surgical management feasible then Orbital exenteration and Debridement of the paranasal sinuses (turbinectomy, palatal resection, medial orbital wall resection). If surgery not feasible, supportive treatment is the option

Prognosis

Mortality rates associated with Mucor mycosis were as high as 90 percent. The disease continues to have high mortality rates, with one study reporting a range of 50 to 80 percent [1]. Another study reviewed 929 Mucor mycosis cases and found the survival rate to be 61 percent in cases treated only with amphotericin B, 57 percent in those treated only with surgery, and 70 percent in those treated with both surgery and amphotericin B [9]. The survival rate may also depend on the number of sinuses that have been infected and the extent to which they are infected.

Prevention of ROCM

In COVID-19 era, it may be possible to reduce the incidence of ROCM by optimizing the indications for systemic corticosteroids, judicious use of tocilizumab, metabolic control, and by minimizing the patient exposure to potential sources of infection.

There may be a role for prophylactic oral Posaconazole in high risk individuals.

Conclusion

Patients getting COVID 19 infection should be made aware of any of the symptoms of ROCM especially who are home isolated. At the time of patient stay in the hospital judicious use of steroids and immunosuppressant can help. At the time of the discharge of the high risk patient, the ENT examination can be conducted there and then to rule out ROCM. If suspected aggressive management is mandatory otherwise this is lethal infection and patient may survive COVID 19, but cannot survive ROCM. In some cases ophthalmologist may be the first physician to see such cases, high index of suspicion will be helpful for early diagnosis and management of this fatal disease.

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