A review of Rhino-orbitocerebral mucormycosis IN COVID

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Abstract

This is a review article. We have collected data from the pubmed, through the various articles published since the inception of COVID-19 in 2019 to October 2021. Rhino-orbital-mucormycosis (ROCM) is increasingly reported in COVID 19 patients, either during or after the recovery from the disease. It is a fulminating infection involving nasal mucosa, paranasal sinuses, further involving orbit and the brain. The major underlying pathology is the immunocompromised status of the patient and aggressive nature of the fungus. The patients present with spectrum of signs and symptoms depending on the stage of involvement. The diagnosis can be done by various microbiological tests and the treatment depends upon the stage of the disease. The mainstay of treatment involves reversal of the patient's immunocompromised state, aggressive treatment with systemic antifungals and surgical debridement. The prognosis is usually grave if diagnosis is delayed. We are still learning about the ROCM in COVID19, and have summarized the available information about the disease.'

Introduction

Mucormycosis (zygomycosis) is a known invasive fungal infection, often acute and extremely severe caused by opportunist and ubiquitous fungi belonging to class phycomycetes, subclass zygomycetes, orderMucorales, family mucoraceae. It is usuallycaused by following species- Absidiacorymbifera, Apophysomyces elegans, Cunning hamellaber tholettieae, Mucor rouxii, Rhizomucorpussillus, Rhizopus arrhizus and by species of genus saksenaea species. [1]

It is acquired by establishment or implantation of fungal spores in the oral, nasal and conjunctival mucosa (Rhino-orbito-cerebral), by inhalation (pulmonary), or by the ingestion of contaminated food (digestive). [1]

As they colonize in nutrients rich in simple carbohydrates being glucose its main energy source. [1]

Mucormycosis is an angioinvasive infection; diabetes mellitus is being reported as most common underlying condition and an independent risk factor of Rhino-orbito-cerebral mucormycosis, being Rhizopus species is the most common cause. [1]

Rhino-orbito-cerebral mucormycosis (ROCM) typically originates in the nasal or oral mucosa, spread to the paranasal sinus and enters the orbit via the ethmoid and maxillary sinuses or via the nasolacrimal duct. Intracerebral extension may occur from the orbit via orbital apex, orbital vessels or via the cribriform plate, carotid artery or possibly via a perineural route. [2]The fungus is angioinvasive and exhibits a remarkable affinity for arteries and grows along internal elastic lamina causing thrombosis and infarction. [3]

The pathogenic mechanisms implicated in the fungal aggressiveness are the decrease of phagocytic functions, ketoacidosis in diabetes offers advantage to this fungal invasion, acidicmilieu reduce binding of iron to transferrin, more available iron due to displacement of protons by transferrin in diabetic ketoacidosis and fungal heme oxygenase which facilitates iron uptake for its metabolism[1], also lack of a dialysable inhibitory factor in patients with diabetes offer favourable conditions for fungal multiplication.[2]

Mucorales have a ketone reductase enzyme, they thrive in hyperglycemia and diabetic ketoacidosis states associated with poor prognosis.[4]

Other common risk factors are immunosuppressive therapy, leukemia, neutropenias , patients with neutrophil dysfunction , hematopoietic stem cell transplantation , diabetic ketoacidosis, iron overload and HIV/AIDS are some identifiable risk factors.[3]

Rhino-orbital involvement is a time sensitive condition that must be recognized and treated promptly to avoid morbidity and mortality. [4]

Challenges in treating Rhino-orbito-cerebral mucormycosis is due in part to its underlying pathogenesis in which endothelial cell damage lead to vascular thrombosis decreasing the efficacy of systemic antifungal medication.[5]

Covid

Corona virus disease 2019(COVID-19) is a new disease caused by a novel corona virus (SARS-COV-2) that was first documented in china in December 2019 and has grown into a worldwide pandemic.[6] Pandemic was officially declared by World health organisation (WHO) on march ,11 ,2020.[7]

The severity of disease ranges from asymptomatic infection to respiratory failure and death.[8] It may progress to acute respiratory distress syndrome (ARDS), a condition that increases the susceptibility of pulmonary fungal coinfections.[9] Severe COVID-19 is associated with immune dysregulation affecting both T-helper cell(Th2) and Th1 responses, including the cytokine release syndrome, which contribute to lung pathology and promote pulmonary microbial proliferation and a subsequent infection.[7]Critically ill covid-19 patients have higher pro-inflammatory (IL1,IL2,IL6,Tumor necrosis alpha) and anti-inflammatory (IL4,IL10) cytokine levels, less CD4 interferon-gamma expression and fewer CD4 and CD8 cells. The immune dysregulation and altered cytokine profile increase the risk of invasive fungal infections (IFI),such as invasive pulmonary aspergillosis(IPA),rhino-orbital cerebral mucormycosis, invasive candidiasis(IC), or pneumocystis jirovecii pneumonia(PJP).[7]

Drugs like methylprednisolone and dexamethasone are believed to modulate inflammation mediated lung injury and thereby reduce progression of respiratory failure in COVID-19.There side effects include increased secondary infections, immune modulation, manifestation of latent diabetes mellitus, dizziness, weight gain, mood changes, insomnia, and muscle weakness.[2]

Although COVID-19 primarily affects the lungs, different disease complications affecting the whole body such as myocardial injury, arrythmia, thromboembolic events and immune dysregulation are reported. [4]

Rhino-orbitocerebral Mucormycosis More In Covid,why?

The second wave of the COVID-19 pandemic in India documented an increase in mucormycosis especially ROCM [10].Critically ill COVID-19 patients are candidates are at a high risk for ROCM and other fungal infections. [9]Most people affected by COVID-19 are old and have other predisposing conditions like type 2 diabetes mellitus.[4]In addition to these patients frequently receive broad spectrum antibiotics and corticosteroids.[4]Also, they are supported by invasive or non-invasive ventilation due to severe ARDS.[4]

Immune dysregulation associated with COVID-19 with reduced number of CD4+T and CD8+T cells, may alter innate immunity. [11] The risk of hospital acquired infections and systemic immune alterations of COVID-19 infection may lead to secondary fungal infections. [11]

On contrary, Clinical evidence suggests that the neutrophils monocytes and macrophages which play a predominant role in the primary host defence against Muckrakes are unaffected in COVID-19 infection, thus eliminating their role in the pathogenesis [12]. On the contrary, an increase in peripheral neutrophil number was noted in COVID-19 with an increased neutrophil lymphocyte ratio [13]. This is in fact beneficial as far as

immunity toward Mucorales is concerned. These neutrophils are very effective and readily inactivate the fungus by the generation of oxidative metabolites if the host is immunocompetent. Analyzing the existing literature lymphopenia seems to be the only significant immune cell defect detected in COVID-19 [12]. However, lymphopenia does not play any significant role in increasing the host susceptibility to Mucorales. Clinically, this can be explained by the lower incidence of mucormycosis in HIV-infected patients and other lymphopenic syndromes. A retrospective study has shown only 2 cases of mucormycosis in autopsy of 1630 patients died of AIDS-related complications from 1984 to 2002, signifying the rarity of incidence [14].

A complex interplay of these multiple factors is probably responsible for increased incidence of ROCM. [11]

It is not necessary that only long term use of corticosteroids in covid patients leads to fungal infection many case reports recently proved that short course of steroids therapy causes mucormycosis[15] especially in people with DM[16,17].

HOW DO THESE PATIENTS PRESENT? [4, 18]

Signs and symptoms of ROCM depend on the stage of the disease at presentation. Honavar SG *et al* [18] have proposed a detailed classification for ROCM. (Table 1)

Proposed staging of RHINO-ORBITO-CEREBRAL MUCORMYCOSIS (ROCM) (Table - 1) [18]

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
Stage 2	**Involvement of paranasal sinuses**
2a	One sinus
2b	Two ipsilateral sinuses
2c	>Two ipsilateral sinuses and/or palate/oral cavity
2d	Bilateral paranasal sinuses involvement or involvement of zygoma or mandible
Stage 3	**Involvement of 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 superior orbital fissure, inferior orbital fissure, orbital apex, loss of vision
3d	Bilateral orbital involvement
Stage 4	**Involvement of 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 skull base, internal carotid artery occlusion, brain infarction
4d	Multifocal or diffuse CNS disease

If only nasal mucosal involvement i.e. patient is in stage-1 of ROCM, the presenting symptoms are nasal discharge, nasal stuffiness, foul smell, epistaxis and signs are like foul smelling sticky mucoid or black tinged or granular or hemorrhagic nasal discharge, nasal mucosal inflammation, erythema, violaceous or blue discolouration, pale ulcer, anaesthesia, ischemia and/or eschar formation.

When there is paranasal sinus involvement i.e. disease is in stage-2, the patient presents with signs and symptoms of stage-1 plus symptoms like-facial pain, facial edema, dental pain, systemic symptoms(fever, malaise) and signs include unilateral or bilateral localises or diffuse facial edema, edema localised over sinuses, localised sinus tenderness.

When there is orbital involvement i.e. disease is in stage-3, patient may also have pain in eye, proptosis, ptosis, diplopia, loss of vision, infraorbital and facial V1 and V2 nerve anaesthesia and signs include 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.

Ophthalmic (V1) and maxillary (V2) nerve anaesthesia and features of 3, 4, 6 nerve palsy indicating orbital apex/superior orbital fissure syndrome may be seen in some patients.

Involvement of the CNS occurs most frequently (70%) due to contiguous spread from the paranasal sinuses and orbits. The remaining 30% are divided equally between isolated CNS infection (usually in intravenous drug injectors) and hematogenous spread from distant sites of infection. Intracranial fungal granuloma is a distinct clinical entity, with most cases to date reported from India. About half the cases are associated with fungal sinusitis, and half appear as isolated intracranial infections with no clinically apparent sinus disease. Aspergillus spp. are the most frequently recovered organisms, followed by Mucorales. Imaging (CT scan and MRI) shows multiple tumour-like masses with faint contrast enhancement and surrounding parenchymal edema. The frontal lobes are the most frequent location. Involvement of central nervous system causes bilateral proptosis, paralysis, altered consciousness, focal seizures and signs include V1 and V2 nerve anaesthesia, ptosis and features of 3,4,6 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 indicates cavernous sinus thrombosis.

Hemiparesis, altered consciousness and focal seizures indicate brain invasion and infarction.

DIAGNOSIS

The clinical diagnosis of mucormycosis by Smith and Krichner[19] criteria include:

(i) Black, necrotic turbinate's

(ii) Blood-tinged nasal discharge and facial pain, both on the same side,

(iii) Soft peri-orbital or peri-nasal swelling with discoloration and induration,

(iv) Ptosis of the eyelid, proptosis of the eyeball and complete ophthalmoplegia and,

(v) Multiple cranial nerve palsies unrelated to documented lesions.

The diagnosis can be done by microbiological examination of nasal mucosal biopsy and imaging. [4, 18]

Nasal endoscopy

Deep or endoscopy guided nasal swab, paranasal sinus or orbital specimen is collected. Direct microscopy of the sample using KOH mount and calcofluor white shows aseptate ribbon like hyphae, wide angle of non- dichotomous branching (more than or equal to 45-90^0) and greater hyphal diameter (6-25 micrometer).Direct microscopy has 90% sensitivity.

The sample can also be cultured on brain heart infusion agar, potato dextrose agar, or sabouraud dextrose agar with gentamicin or chloramphenicol and polymyxin B but without chlorhexidine, incubated at 30-37^{0}C.This is strongly recommended andcan help in genus and species identification and antifungal susceptibility testing.Rapid growth of fluffy white, grey or brown cotton colonies can be seen. The sample can also be used for molecular diagnosis by

quantitative polymerase chain reaction(75% sensitivity) and can be used for diagnosis confirmation.

Histopathology of the sample is done with haematoxylin-eosin, Periodic-acid-Schiff and Grocott-gomori'sMethanamine-silver special stain. Hyphae showing tissue invasion is confirmatory of invasive ROCM.[13]

Imaging – Contrast enhanced MRI preferred over CT scan

Nasal and paranasal sinus mucosal thickening with irregular patchy enhancement is an early sign of ROCM. Also, Ischemia and non-enhancement of turbinates manifests as an early sentinel sign on MRI-described as the Black turbinate sign. The fluid level in sinus and partial or complete sinus opacification signifies advanced involvement of paranasal sinus.Thickening of medial rectus is an early sign of orbital invasion.

Patchy enhancement of orbital fat,lesion in the area of superior and inferior orbital fissure and the orbital apex and bone destruction at the paranasal sinus and orbit are seen with advancedstages of the disease. The stretching of optic nerve and tenting of posterior pole of eyeball indicate severe inflammatory edema secondary to tissue necrosis.

MR Imaging and angiography

These help determine the extent of soft tissue involvement, intracranial extension, cavernous sinus involvement and ischemic damage to CNS.MRI with diffusion weighted imaging may also show us the cerebral infarcts.

MANAGEMENT OF RHINO-ORBITO-CEREBRAL MUCORMYCOSIS[4, 18]

Management depend on the stage of the disease and whether it is possible, probable or proven Rhino-orbito-cerebral mucormycosis. The treatment recommendations can be supported by the global guidelines for the diagnosis and management of mucormycosis in 2019 by European Confederation of Medical Mycology (ECMM) and Mycoses Study Group Education and Research Consortium.[20]

Possible ROCM: These patients havesigns and symptoms of ROCM and the risk factors including less than 6 weeks treated COVID-19, Diabetes mellitus, immunosuppression, use of systemic steroids or Tocilizumab, Mechanical ventilation or supplemental oxygen.These patients should be given.Supportive treatment and kept under observation. Nasal endoscopy is repeated after 24hour and with contrast enhanced MRI or CT scan after 72 hours.If patient improves and there is no evidence on endoscopy or imaging then just continue observation for 3 weeks. On the other hand,if there is evidence on endoscopy or biopsy then manage it as a case of probable ROCM.

Probable ROCM patients: They have signs and symptoms plus there is supportive evidence clinically and on diagnostic nasal endoscopy and/or contrast enhanced MRI/CT scan.

Proven ROCM patients: have signs and symptoms plus there is supportive evidence clinically and on diagnostic nasal endoscopy and/or contrast enhanced MRI/CT scan and also there is confirmation on direct microscopy or histopathology with special stains or molecular diagnosis.

For both possible and proven ROCM patients

Immediate induction therapy with intravenous Liposomal Amphotericin-B (5-10 mg/kg body weight) for a minimum of 4weeks followed by oral isavuconazole (200mg TDS on day 1-2 and 200mg OD from day 3) or oral Posaconazole (300mg BD on day 1 followed by 300mg OD from day 2).The oral drugs are given for a duration of3-6 months (minimum of 6 weeks).

If amphotericin B is not available, Amphotericin B lipid complex (ABCL)can be used but its side effects are more prominent. Also, if Amphotericin B is contraindicated, intravenous Isavuconazole (200mg TDS on day 1-2 followed by 200mg OD from day 3)or intravenous Posaconazole (300mg BD on day 1 followed by 300 mg OD from day 2) can be used.

With this if there is sino-nasal involvement, early and aggressive MRI/CT guided debridement of paranasal sinus is done (with or without Turbinectomy, palatal resection and medial orbital wall resection) with clean

margins. Alongwith this, Retrobulbar Amphotericin B (3.5mg/ml) and sinus irrigation with Amphotericin B (1mg/ml) can also be given.

If there is worsening of orbital component in less than or equal to 72hr, then orbital exenteration can be considered along with above measures.

If CNS is involved surgery is done if systemic condition permits (orbital exenteration+ aggressive debridement of paranasal sinus+ turbinectomy+ palatal resection + orbital wall resection)with clean margins along with supportive treatment.

And if surgery is not feasible then only supportive treatment is done.

In neutropenic patients, those with graft-versus-host disease or high risk factors, primary prophylaxis with posaconazole may be recommended(ECMM and Mycoses Study Group Education and Research Consortium).[20] However, no such recommendations have been givenfor severely ill COVID patients, and may be given by physician based on his assessment.

PROGNOSIS

Survival in mucormycosis depends on early diagnosis, alleviation of basic predisposing factors, aggressive debridement of necrotic tissues and appropriate systemic antifungal agents. [8]

Mortality rate in ROCM is as high as 90% [10]. Approximately 50% of cases of mucormycosis have been diagnosed in autopsy [10]. This prompted us to conduct a systematic review of published case reports/series of mucormycosis in people with COVID-19, to know its temporal associations in relation to comorbidities, association with drugs being used in COVID-19 and overall characteristics of patients with its outcome. We additionally postulated a mechanistic explanation as to why mucormycosis could be increasingly linked to COVID-19 and is being reported increasingly from India. Predisposing factors such as corticosteroid therapy should be discontinued and blood sugar should be controlled restrictively. [8] ROCM in case of brain involvement, mortality rises to 50%-85%. [8]

Prognosis is dependent on multiple factors and early initiation of treatment is an important element. [11]A delay of even 6 days is associated with a doubling of 30day mortality from 35%-65%.[10]Once the diagnosis is confirmed conservative management is started for the patient.[11]Orbital exenteration remains the most difficult decision in Rhino-orbital cases, due to concerns about disability and disfigurement. Although exenteration is the last resort, but can be life saving in a few cases. [11]

CONCLUSION

COVID-19 is associated with a significant increased incidence of fungal infections due to Immune dysregulation. Additionally, the widespread use of steroids/Tocilizumab/broad spectrum antibiotics for treating COVID-19 may lead to development/exacerbation of preexisting fungal infection.Diabetes which is the most important risk factor for ROCM, is exacerbated in COVID-19 due to steroid induced hyperglycemia.There is increased risk of fungal infection in patients with pre-existing risk factors.Early diagnosis and treatment should be done as it leads to subsequent reduction of morbidity and mortality due to rhino orbito cerebral mucormycosis and improves the prognosis.

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