Acta Scientific Otolaryngology (ISSN: 2582-5550)

Volume 4 Issue 4 April 2022

Review Article

Covid Associated Mucormycosis: What do we Know Till Now?

Vikasdeep Gupta[1] and Vandana Sharma[2]*

[1]*Department of Ophthalmology, All India Institute of Medical Sciences (AIIMS), Bathinda, India*

[2]*Department of Ophthalmology, Adesh Institute of Medical Sciences and Research (AIMSR), Bathinda, India*

***Corresponding Author:** Vandana Sharma, Department of Ophthalmology, Adesh Institute of Medical Sciences and Research (AIMSR), Bathinda, India.

Received: March 14, 2022

Published: March 28, 2022

Abstract

COVID 19 pandemic has overburdened the healthcare infrastructure in India in the last few months. As the second wave recedes, mucormycosis emerged as a new nemesis which is life and vision threatening to the already immunocompromised post COVID patients. This review article is written with the intent to identify a definitive approach towards early identification of the disease and to formulate guidelines for prompt management.

Keywords: Mucormycosis; COVID-19; Infrastructure

Introduction

In the COVID era various states in India declared a situation of epidemic due to an alarming increase in incidence of mucormycosis not only in active COVID cases but also as a late complication in recovered cases of COVID, irrespective of the disease severity. Thus, it became imperative to analyse the information collected regarding mucormycosis in the COVID era and amalgamate it with the pre-existing knowledge regarding the disease.

Methodology

The authors searched PUBMED with the following search terms "COVID-19" "AND", "rhino-orbital-cerebral mucormycosis", "diagnosis", "medical management" and "surgical management". The search was restricted to manuscripts in English language and till May 8th, 2021. After removing duplications, commentaries, opinion letters and manuscripts not relevant to mucormycosis, other newer manuscripts from cross-references were added and a synopsis of the data collected from these manuscripts is provided below.

Results

Mucormycosis is a form of invasive fungal infection that may prove to be life-threatening and typically affects immunocompromised individuals with an impaired neutrophilic response. Persons with uncontrolled diabetes mellitus, haematological malignancies, acquired immunodeficiency syndrome, iatrogenic immunosuppression, such as those who have undergone organ transplantation are at an increased risk of infection [1].

Incidence

The incidence of mucormycosis in pre-covid era was reported as low as 0.079- 0.95 cases per 10,000 patient days from 1999-2004 [2]. Saegeman., *et al*. also reported an incidence of 0.042/10,000 patient days with a peak incidence of 0.15/10,000 patient days in 2006 over eight study years [3]. Chamilos., *et al*. reported that the incidence rate of mucormycosis in pre covid era varied from 0.005 to 1.7 per million population and a delay of even 6 days in diagnosis and management was found to be associated with a doubling of 30-day mortality rate from 35% to 66% [13].

A slow rise in the incidence of mucormycosis was already reported in the pre COVID times by various authors which was attributed to increase in the incidence of diabetes mellitus, rate of allogenic organ transplantations, increased prophylactic use of voriconazole and hematological malignancies [4-9].

COVID era has seen a sudden surge in the number of invasive fungal infections especially mucormycosis. White., *et al*. studied 135 adults with Covid-19 infection and reported an incidence of 26.7 per cent for invasive fungal infections [10]. A similar surge in number of invasive fungal infection was reported from China and Italy as early as April 2020 [11].

Invasive mucormycosis most commonly presents as rhino-cerebro-orbital mucormycosis (ROCM) (44-49%), followed by cutaneous (10-19%), pulmonary (10-11%), disseminated (6-11%) and gastrointestinal (2-11%) manifestations [12].

Risk factors

Several factors have been attributed to this increased incidence of mucormycosis. A dysregulated immune response secondary to infection by the SARS CoV-2 virus generates a robust inflammation and concurrent immunosuppression which in turn provides a hospitable environment for the development of fungal co-infections [11]. SARS-CoV2 induced lymphopenia and altered neutrophil: lymphocyte ratio also explains the immunosuppression in patients with no history of steroid intake during covid illness or diabetes. This increases the severity of the viral infection further and also renders the patient susceptible to invasive fungal co-infections [14].

The aggressiveness of the otherwise ubiquitous and docile fungi is also increased due to various factors such as a decrease in phagocytic function of neutrophils and macrophages and increased availability of iron due to displacement of protons by transferrin in diabetic ketoacidosis. As the fungal heme oxygenase facilitates iron uptake for its metabolism, increased availability of free serum iron provides a nutritional haven for the fungus to grow unchecked [15]. The pathogenesis of Covid-19 additionally resembles the spectrum of thrombotic microangiopathies causing angioinvasion and endothelial damage. This is quite synergistic to the mechanism of action of the mucorales thereby aggravating the disease [16].

Presenting features

ROCM is a typical presentation in diabetic patients whereas patients with profound neutropenia and graft-versus-host disease develop pulmonary mucormycosis [17]. Presenting signs and symptoms in cases of ROCM are summarised in table 1 [18,19].

Symptoms	Signs
Headache	Orbital cellulitis
Fever	Palpebral oedema
Loss of touch sensation over cheek region or nasal mucosa	Ptosis
Unilateral facial swelling	Chemosis
Sudden prominence of eyeball	Ophthalmoplegia
Diplopia	Necrotic eschar in nasal cavity
Sudden loss of vision	Purulent or blood-tinged nasal discharge
Nasal discharge	

Table 1: Summarising presenting symptoms and signs of ROCM.

Anaesthesia felt over cheek region or nasal mucosa is an early sign as well as symptom of invasive mucor infection and it should prompt biopsy and culture in at risk patients for mucormycosis. Black necrotic eschar tissue that resembling dried blood or a purulosanguinous exudates with an unpleasant odour may be observed in the nasal cavity in mucormycosis [19].

As the fungal infection spreads locally it may invade the orbit from the nasal cavity or paranasal sinuses via the lamina papyracea, inferior orbital fissure, superior orbital fissure, infra-temporal fossa or the orbital apex. Therefore, the patient presents with ocular complaints ranging from decreased vision as the primary complaint to mono-muscular palsy leading to diplopia as the earliest symptom. Late features include complete blindness, chemosis/proptosis, total ophthalmoplegia and optic atrophy on ophthalmoscopy. Headache, altered consciousness and death may result from further spread from orbit to the intracranial space [20].

Diagnosis

As clinical presentation can be variable, a definitive diagnosis can be made by a multidisciplinary approach with microbiological, histological, and radiological examination in addition to nasal endoscopic examination.

KOH mounts of nasal scrapings taken endoscopically can be used as a screening tool. Fungal hyphae will be visualised which are wide, non-septate and measure 10-20 µm in diameter, with filaments branching from main body at almost 90°. However, confirmation with histopathological examination of excised tissue is a must. Frozen section examination of debrided tissue is traditionally preferred over paraffin as it provides rapid processing and overall higher sensitivity and specificity. But this approach must be discarded in the setting of concurrent COVID infection. In such cases formalin-fixed paraffin-embedded processing is preferred as the high temperatures needed in the process may inactivate the virus thus reducing chances of spreading COVID to the handling staff [21,22]. Histopathological findings will show the broad aseptate fungal hyphae along with direct fungal invasion into blood vessels, vasculitis with thrombosis leading to tissue infarction, haemorrhage, and acute neutrophilic infiltrate [23].

Quantitative PCR for specific markers for Mucorales species can confirm diagnosis serologically. It can also predict the survival rate which was found to be significantly higher in patients with an initially positive PCR result that became negative after treatment initiation than in patients whose PCR result remained positive [24].

From the radiological point of view, Computed Tomography (CT scan) and Magnetic Resonance Imaging (MRI) may be employed. In the early stages CT mucosal thickening can be seen along with absence of air-fluid level in the infected sinus. This may be later on followed by destruction of medial orbital wall and invasion of rectii, orbital apex and ipsilateral cavernous sinus. MRI in a case of ROCM may show a hyperintense sinus wall, T2-W hyperintense lesion extending from paranasal sinus along orbital apex into intracranial structures and narrowing or slow flow in the ipsilateral internal carotid artery in the vicinity of mucor invasion [25].

Treatment

Surgical and medical management has to go hand in hand in such cases. Surgical debridement of all the necrosed tissue along with intravenous administration of Amphotericin-B in a dose of 5-10 mg/kg/day for a total dose of 2-3g is the treatment of choice. However, orbital involvement complicates the decision making regarding surgical debridement. Bradoo., *et al*. have proposed a scoring system, the Sion hospital scoring system, to help in deciding when a patient needs orbital exentration [20].

Endoscopic Orbital Exenteration is a newer concept where the orbit is exenterated via the trans-nasal route. In this technique the uninvolved superior and lateral periorbita can be preserved. It has numerous operative and post-operative benefits namely [26]:

- Direct trans-nasal cauterization of the Ophthalmic artery as it emerges from the Optic foramen
- Better visualization of the extent of disease in the orbit.
- Avoids post-operative packing of the orbital cavity
- Post-operative mucosalization of the cavity is better
- No need of tissue-grafting for reconstructive procedures.

Medical management consists primarily of Amphotericin B which is a polyene amphoteric macrolide with internal cyclic ester and 4-7 conjugated double bonds. It is poorly soluble in aqueous media and this micellar or liposomal formulations are used for better tissue penetration [27]:

- Conventional Amphotericin-B
- Amphotericin-B Colloidal Dispersion
- Liposomal Amphotericin-B
- Amphotericin-B Lipid complex.

However, Amphotericin B can cause several side effects which can be drug related, infusion related or hematological. To avoid infusion related complications such as nausea, tachypnoea, stridor etc, pre-medication with anti-pyretics, antihistamines and corticosteroids should be given. Further giving a prior test dose of 1 mg IV and giving the infusion slowly may prevent these reactions [20].

Nephrotoxicity is a direct drug related adverse effect of amphotericin B which can further lead to anemia due to erythropoietin deficiency. Pre-loading the patient with 1 litre of normal saline prior to amphotericin infusion helps to reduce the nephrotoxicity. Hypokalaemia, hyponatremia and hypomagnesaemia should be treated as soon as possible. Anemia is transient and can be managed with recombinant erythropoietin till the drug is being administered [28].

A combination therapy with echinocandins and amphotericin B is a second-line therapy which may be used in cases showing no response to monotherapy with amphotericin B. combination

of echinocandins with amphotericin B adds a polyene backbone, which increases the success of therapy.

Other second-line antifungals which may be considered include the triazoles namely posaconazole and isavuconazole. Triazoles inhibit the 14-á-demethylation, which leads to an increase in toxic 14-á-methylsterols that alters the fungal membrane's permeability. Patients intolerant to amphotericin B such as those with severe nephrotoxixity, pre-existing diabetic nephropathy etc may be given Posaconazole in a dose of 400 mg once a day in syrup form. Isavuconazole is mostly used in the treatment of invasive mucormycosis [29].

Supplementary therapy with deferasirox, an oral iron chelator has shown beneficial results in controlling Mucorales through iron starvation [30,31].

Conclusion

Mucormycosis is an aggressive disease which has become deadlier in the COVID times. ROCM is the most common presentation. Timely diagnosis and aggressive management can be vision and life saving for the patient. A multidisciplinary approach is indispensable. Management of underlying predisposing factors along with surgical debridement and antifungal therapy is the crux of the treatment regimen.

Bibliography

1. Sharma S., *et al*. "Post coronavirus disease mucormycosis: a deadly addition to the pandemic spectrum". *Journal of Laryngology and Otology* 135.5 (2021): 442-447.

2. Kontoyiannis DP., *et al*. "Zygomycosis in a tertiary-care cancer center in the era of Aspergillus-active antifungal therapy: a case-control observational study of 27 recent cases". *Journal of Infectious Disease* 191.8 (2005): 1350-1360.

3. V Saegeman., *et al*. "Epidemiology of mucormycosis: review of 18 cases in a tertiary care hospital". *Medical Mycology* 48.2 (2010): 245-254.

4. Chayakulkeeree M., *et al*. "Zygomycosis: the re-emerging fungal infection". *European Journal of Clinical Microbiology and Infection Disease* 25.4 (2006): 215-229.

5. Kauffman CA. "Zygomycosis: reemergence of an old pathogen". *Clinical Infectious Diseases* 39.4 (2004): 588-590.

6. Safdar A., *et al*. "Efficacy and feasibility of aerosolized amphotericin B lipid complex therapy in caspofungin breakthrough pulmonary zygomycosis". *Bone Marrow Transplantation* 34.5 (2004): 467-468.

7. Marr KA., *et al*. "Epidemiology and outcome of mould infections in hematopoietic stem cell transplant recipients". *Clinical Infectious Diseases* 34.7 (2002): 909-917.

8. Roden MM., *et al*. "Epidemiology and outcome of zygomycosis: a review of 929 reported cases". *Clinical Infectious Diseases* 41.5 (2005): 634-653.

9. Chakrabarti A., *et al*. "Ten years' experience in zygomycosis at a tertiary care centre in India". *Journal of Infection* 42.4 (2001): 261-266.

10. White L., *et al*. "A national strategy to diagnose coronavirus disease 2019 - associated invasive fungal disease in the intensive care unit". *Clinical Infectious Diseases* (2020): ciaa1298.

11. Gangneux JP., *et al*. "Invasive fungal diseases during COVID-19: we should be prepared". *Journal of Medical Mycology* 30 (2020): 100971.

12. Arnaiz-Garcý´a ME., *et al*. "Cutaneous mucormycosis: report of five cases and review of the literature". *Journal of Plastic, Reconstructive and Aesthetic Surgery* 62 (2009): 434e441.

13. Chamilos G., *et al*. "Delaying amphotericin B-based frontline therapy significantly increases mortality among patients with hematologic malignancy who have zygomycosis". *Clinical Infectious Diseases* 47 (2008): 503-509.

14. Liu J., *et al*. "Longitudinal characteristics of lymphocyte responses and cytokine profiles in the peripheral blood of SARSCoV- 2 infected patients". *EBioMedicine* 55 (2020): 102763.

15. Waizel-Haiat S., *et al*. "A Case of Fatal Rhino-Orbital Mucormycosis Associated With New Onset Diabetic Ketoacidosis and COVID-19". *Cureus* 13.2 (2021): e13163.

16. Sweeny JM., *et al*. "Evidence for secondary thrombotic microangiopathy in COVID-19". *MedRxiv preprint* (2021).

17. Vandroux D., *et al*. "Mortality of critically ill patients with severe influenza starting four years after the 2009 pandemic". *Infectious Disease* 51.11-12 (2019): 831-837.

18. Scheckenbach K., *et al*. "Emerging therapeutic options in fulminant invasive rhinocerebral mucormycosis". *Auris Nasus Larynx* 37 (2010): 322e328.

19. Singh VP., *et al*. "Sinonasal Mucormycosis: A to Z". *Indian Journal of Otolaryngology and Head and Neck Surgery* 71 (2019): 1962-1971.

20. Shah K., *et al*. "Orbital Exenteration in Rhino-Orbito-Cerebral Mucormycosis: A Prospective Analytical Study with Scoring System". *Indian Journal of Otolaryngology and Head and Neck Surgery* 71.2 (2019): 259-265.

21. Mekonnen ZK., *et al*. "Acute Invasive Rhino-Orbital Mucormycosis in a Patient With COVID-19-Associated Acute Respiratory Distress Syndrome". *Ophthalmic Plastic and Reconstructive Surgery* 37.2 (2021).

22. E Bouza., *et al*. "Mucormycosis: an emerging disease?" *Clinical Microbiology and Infection* 12 (2006): 7-23.

23. DeShazo RD., *et al*. "Fungal sinusitis". *The New England Journal of Medicine* 337 (1997): 254-259.

24. Millon L., *et al*. "Early diagnosis and monitoring of mucormycosis by detection of circulating DNA in serum: retrospective analysis of 44 cases collected through the French Surveillance Network of Invasive Fungal Infections (RESSIF)". *Clinical Microbiology and Infection* 22 (2016): 810.e1-810.e8.

25. Lone PA., *et al*. "Rhino-orbito-cerebral mucormycosis: Magnetic resonance imaging". *Indian Journal of Otology* 21 (2015): 215-218.

26. Radner AB., *et al*. "Acute invasive rhinocerebral zygomycosis in an otherwise healthy patient: case report and review". *Clinical Infectious Diseases* 20 (1995): 163-166.

27. Piromchai P and Thanaviratananich S. "Impact of treatment time on the survival of patients suffering from invasive fungal rhinosinusitis". *Clinical Medicine Insights: Ear, Nose and Throat* 7 (2014): 31-34.

28. Walsh TJ., *et al*. "Amphotericin B lipid complex for invasive fungal infections: analysis of safety and efficacy in 556 cases". *Clinical Infectious Diseases* 26 (1998): 1383-1396.

29. Riley TT., *et al*. "Breaking the mold: a review of mucormycosis and current pharmacological treatment options". *Annals of Pharmacotherapy* 50.9 (2016): 747-757.

30. Lewis RE., *et al*. "Activity of deferasirox in Mucorales: influences of species and exogenous iron". *Antimicrobial Agents and Chemotherapy* 55 (2011): 411-413.

31. Ibrahim AS., *et al*. "The iron chelator deferasirox protects mice from mucormycosis through iron starvation". *Journal of Clinical Investigation* 117 (2007): 2649-2657.