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Presentation of mucormycosis in post Covid-19 infected patients and an approach to its management in a tertiary care centre of central India

Sameeksha Mishra[1,*], **Dhaval Bhojani**[1], **Sudhakar Vaidya**[1]

[1]*Dept. of ENT, RD Gardi Medical College, Ujjain, Madhya Pradesh, India*

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ABSTRACT

Background: This is a case study of 70 cases admitted in our hospital post covid-19 infection with different complaints and signs and symptoms indicating Rhino-Orbital-Cerebral-mucormycosis (ROCM).
Materials and Methods: All the cases were again screened for COVID infections and comorbidities like Diabetes mellitus, Hypertension or any other immunocompromised state. The level of involvement like nasal cavity, septum, turbinates, sinuses, pterygopalatine fossa, palate, orbit or any cerebral involvement was noted and the protocol of medical and surgical management was decided in accordance to that. Post surgery KOH mount and HPE report, CT and MRI findings were the major pillars in this regard.
Results: In 100% of cases we did middle meatus antrostomy with partial middle turbinectomy and in 57% cases we did medial maxillectomy with Modified Denker's.Rest middle meatus mega antrostomy with ethmoidectomy with partial middle turbinectomy & full house FESS was done in 21% of cases.
Conclusion: The first step in the management of mucormycosis is to have a high index of clinical suspicion especially in those with COVID- 19 who have diabetes mellitus, and who have received systemic corticosteroids while on treatment.

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1. Introduction

Mucormycosis a fungal infection is caused by a group of fungi called mucormycetes which are naturally found in air, water and even food. It enters in the body through inhalation of fungal spores from the air and commonly affects sinuses and lungs. It infects the nose, orbit of eye, oral cavity and can even spread to the brain.[1] Symptoms mainly seen are headache, nasal congestion, nasal discharge, bleeding nose, crusting in nose, swelling on face, lack of sensation on face and skin discoloration. Pulmonary and cutaneous variants are also seen. In COVID-19 pandemic where corticosteroids were used in huge amount there was a steep rise in case reports/series of mucormycosis in people especially from India. Fatality rate with mucormycosis was pretty high. Mucormycosis cases were classified as "possible", "probable" or "proven" according to the recently published guideline of "Code Mucor: guidelines for the Diagnosis, Staging and Management of Rhino- Orbito-Cerebral Mucormycosis in the Setting of COVID-19". This describes the rhino-orbito-cerebral mucormycosis and for the patients with involvement other than these, the criterion of "probable" was changed to include organ-specific endoscopic procedures and MRI or CT imaging studies.[2] The occurrence of mucormycosis, in the general population was previously cited as 0.005 to 1.7 per million population before COVID. However, in India the incidence of mucormycosis was reported to be 0.14/1000 in diabetic patients which is 80 times higher than reported in other parts of the world. The large number of diabetic patients in India of almost 62 million, mucormycosis has caused large public health burden in India. An advisory issued by the Indian

* *Corresponding author*.
E-mail address: drsameeksha.06@gmail.com (S. Mishra).

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Council of Medical Research states the following conditions in COVID-19 patients increase the risk of mucormycosis infection: Uncontrolled diabetes, weakening of immune system due to use of steroids, Prolonged ICU/hospital stay, co-morbidities / post organ transplant / cancer. One hallmark of mucormycosis is angioinvasion. Recently, the glucose regulated protein 78 (GRP78) has been identified to enable invasion of the pathogen via an endocytotic mechanism in various studies.[3] The term mucormycosis can be used interchangeably with zygomycosis. Zygomycota (which comprises of Mucorales, Entomophthorales, and others). The most frequently reported pathogens are Rhizopus spp, Mucor spp, and Lichtheimia spp, followed by Rhizomucor spp, Cunninghamella spp, Apophysomyces spp, and Saksenaea spp. Lichtheimia spp were identified as the major pathogens.[3] In all these populations, an enhanced availability of iron in tissues or serum promoted aggressive invasive growth of acquired spores of Mucorale.

2. Materials and Methods

The study was carried out in our tertiary care centre on patients with post covid-19 Mucormycosis cases. This is a case study of 70 cases admitted in our centre post covid-19 infection with different complaints and signs and symptoms indicating Rhino-Orbital-Cerebral-mucormycosis. All the cases were again screened for covid infections and comorbidities like DM, HTN or any other immunocompromised state. The level of involvement like nasal cavity, septum, turbinates, sinuses, palate, orbit or any cerebral involvement was noted and the protocol of medical and surgical management was decided in accordance to that. Post surgery KOH mount and HPE report, CT and MRI findings were the major pillars in this regard. The diagnosis of COVID-19 was based on any one of the following pre or post mucormycosis: reverse transcription polymerase chain reaction (RT-PCR)test from nasopharyngeal or oropharyngeal swabs, rapid antigen test, or computed tomography (CT) chest scores in the absence of a positive RT-PCR test in a symptomatic case.

2.1. History, signs & symptoms

Table 1: History of patients

Criteria	Covid positive	Diabetes mellitus	Steroid use history
No. of patients	65	55	68

2.2. Management

Suspected mucormycosis needs an urgent intervention, due to rapidly progressive and destructive nature of this infection.[4] The spectra of management of such patients is vast and mainly comprised of diagnostic nasal endoscopy, KOH swab for culture and staining, CT scanning/MRI, blood sugar montitoring and proper control and dealing with any other systemic or immunocompromised state. Then the first and most important surgical steps following the diagnosis for successful infection management and improved survival rate was aggressive surgical debridement followed by repeated suction and cleaning of cavity and local application of amphotericin ointment was done. So, it can be said that the general management comprised of radical debridement and excision of the infected tissues with a high-dose therapy of amphotericin B. The procedure involved removal of all the necrotic tissue, until perfused tissue was encountered. In many severe cases, orbital exenteration was inevitable. In several other severe cases excision of the nasal cartilage and the palate was also required. In first line of treatment for aspergillosis we prescribed Voriconazole. The early diagnosis and subsequent treatment of invasive mycosis is vital for a favourable for better outcome and prognosis. The poor outcome of such cases is may be due to the severe invasiveness of mycotic infections.[5]

Table 2: Area of involvement

Area of involvement	No. of patients
Nasal	70
Sinuses	60
Ocular	21
Cerebral	24
Palatal	13

2.3. Investigations

Owing to the high mortality of cases of mucormycosis high index of suspicion is needed to ensure timely diagnosis which is helpful to devise appropriate treatment in high-risk populations.[6]

CT PNS AND MRI PNS Findings Showing Involvement of Different Structures

3. Involvement of Sinuses

Table 3: Sinuses involved

Sinuses involved	No. of patients
Maxillary	60
Ethmoid	50
Frontal	15
Sphenoid	10

Fig. 1:

Fig. 2:

Fig. 3:

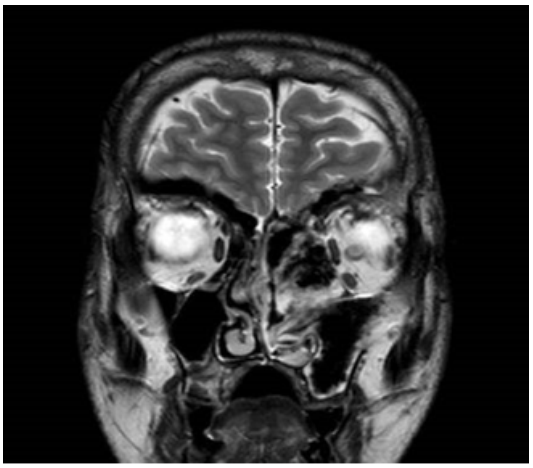

Fig. 4:

4. Surgical Procedure

Table 4: Surgical procedure done

Procedure	No. of Patients
Middle meatus antrostomy with partial middle turbinectomy	70
Middle meatus mega antrostomy with ethmoidectomy with partial middle turbinectomy	15
Medial maxillectomy with Modified Denker's approach	40
Full house FESS	15

5. Post-Surgical Work Up

Repeated debridement with alternate day suction and cleaning, local application of Amphotericin ointment and packing, KOH mount and HPE after every debridement, saline nasal wash, every third day suction & cleaning even after discharge followed by weekly follow up and then monthly, Post surgery CT/MRI, ocular involvement was taken care of and if required exenteration was done in excessive involvement cases by ophthalmology department. Patients with extensive palatal involvement were provided with obturator or prosthesis from the dental department.

6. Results

In this study we have learnt that the management of mucormycosis is a long and tedious job and cannot be achieved in a day or two. As per management what we did at our tertiary care centre 100% patients presented with involvement of maxillary sinus and 71% had their ethmoid sinus involved while only 21% cases had their frontal sinus involved and only 14% cases were seen with sphenoid involvement. So,as per the involvement of areas on CT/MRI findings and DNE, surgical decisions were made and in 100% of cases we did middle meatus antrostomy with partial middle turbinectomy and in 57% cases we did medial maxillectomy with Modified Denker's. Rest middle meatus mega antrostomy with ethmoidectomy with partial middle turbinectomy & full house FESS was done in 21% of cases.The medical management like administration of drugs like Amphotericin-B(50mg/kg) were decided once the extent of infection and involvement was determined in a particular patient. Other resorts like management of blood glucose levels and other comorbidities was of utmost importance in achieving a fruitful result.

7. Discussion

Mucormycosis is extremely rare in healthy individuals but several immunocompromised conditions predispose it which includes uncontrolled Diabetes mellitus with or without Diabetic ketoacidosis, hematological and other malignancies, organ transplantation, prolonged neutropenia, immunosuppressive and corticosteroid therapy, iron overload or hemochromatosis, deferoxamine or desferrioxamine therapy, acquired immunodeficiency syndrome (AIDS).[7] Diabetics with ketoacidosis are more prone as Rhizopus species prefer hyperglycemic environment. Mucorales have a ketone reductase enzyme so, they thrive in hyperglycemic and diabetic ketoacidosis states generally associated with poor prognosis.[8] After infecting the para nasal sinuses spores spread inferiorly to involve the palate, posteriorly into the sphenoid sinus or cranially to attack the brain. Treatment involves mainly Amphotericin-B and surgical debridement. Repeated suction & cleaning is the main stay for this disease. As in majority of cases we have to do middle meatus antrostomy, this does not cause CSF leakage and also minimizes the risk for olfactory dysfunction. The antrostomy window created is large enough to secure drainage and ventilation of the maxillary sinus. Also, the middle meatus, which is now deprived of the antero-inferior aspect of the middle turbinate, enables the patient to irrigate the maxillary sinus with a saline solution. The maxilla is the upper part of the jaw bone. Surgery to remove the maxilla is called a maxillectomy, done in several extensive cases. Denker's and modified Denker's approach proved to be promising in many patients. The modified Denker's approach is an amalgamation of the classical Denker's approach described in 1906 by Alfred Denker and the endonasal procedure described in 1908 by Strurmann and canfield also known by the acronym TEAMM: total endoscopic anterior medial maxillectomy, this is a widely used approach for extensive diseases of the maxillary antrum. Through mucosal cuts in the nasal cavity along the floor and anterior to the middle turbinate, subperiosteal flaps are elevated to expose the anterior maxilla, the infraorbital foramen, and its neurovascular bundle as well as the lateral nasal wall. A bony window is created in the anterior wall and connected to the medial maxillectomy incisions made beforehand. This provides a number of advantages over other endoscopic procedures.[9] There are specific pathophysiologic features of COVID-19 that may cause secondary fungal infections, extensive pulmonary disease and subsequently alveolo-interstitial pathology that enhances the risk of invasive fungal infections.[10]Coronavirus Disease 2019 (COVID-19), during the second wave in early 2021, has caused devastating chaos in India.[11]COVID-19 patients must be followed up beyond recovery to avoid any recurrence.[12] In India with the outbreak of the second wave of COVID-19 and the delta variant of the virus, there has been a steep rise in this opportunistic fulminant fungal infection, called as COVID-associated Mucor mycosis (CAM).[13]

Over one third of patients with ROCM have an undesirable clinical outcome. Uncontrolled diabetes mellitus at presentation, involvement of the orbital apex and the usage of steroids were associated with poorer outcomes as already discussed. CNS involvement was a factor determining mortality.[14] An aggressive multidisciplinary approach is a requisite to reduce mortality.[15]

8. Conclusion

COVID-19 has put the entire world in turmoil situation, and an exact cure for this deadly infection has not been found yet. One more probable reason for the surge in post-COVID mucormycosis is the unhygienic delivery of oxygen or low-quality tubing system at the hospital ICUs and wards, the oxygen cylinders with unclean masks or using contaminated/tap water in humidifiers and prolonged usage of same mask for more than one patients. Apart from

uncontrolled hyperglycemia free unbound iron in serum plays an essential role in the pathogenesis of mucormycosis. The first step in the management of mucormycosis is to have a high index of clinical suspicion especially in those with COVID- 19 who have diabetes mellitus, and who have received systemic corticosteroids while on treatment. Despite aggressive therapy the overall mortality rate is high. ROCM is a super infection that has been dreadful to the society in this covid era as it was an epidemic in an undergoing pandemic. Drug played an important role in this infection, like steroid intake was seen in majority of cases though it was a two edged sword and post covid immense use of Amphotericin-B drug has dramatically effected the renal status of the patients though it was the only main stay.

9. Source of Funding

None.

10. Conflict of Interest

None.

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Author biography

Sameeksha Mishra, Resident https://orcid.org/0000-0002-5367-5483

Dhaval Bhojani, Resident https://orcid.org/0000-0001-9339-3875

Sudhakar Vaidya, Professor and Head

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