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Our Surgical Experience with 300 Cases of Covid Associated Mucormycosis(CAM)

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Abstract:-

Background: The incidence of mucormycosis increased dramatically after the COVID-19 pandemic which was named CAM (covid associated mucormycosis). The number of published articles on mucormycosis increased from 74 in the year 2000 to 786 in the year 2022 [2]. It indicates the increasing disease burden. Mucormycosis prevalence in India is estimated to be 140 cases per million people, which is almost 80 times greater than the incidence in wealthy nations. Death was reported in 389/851 (46%) patients in a systemic review and meta-analysis of 851 case reports published in 2018. In May 2021, several Indian states declared mucormycosis a notifiable disease in response to the rise in COVID-19-associated mucormycosis [1].

Methods: For all the patients who are suspected to have mucormycosis, nasal scrapings were taken under endoscopic guidance and sent for KOH mount and culture. Regardless of the microbiological evidence, based on diagnostic nasal endoscopic findings alone we subjected all patients to MRI brain and PNS and Orbits multiplanar fat-suppressed images with and without contrast. A sum of 300 patients who are confirmed to have mucormycosis early or late in the course of treatment and for which who received surgical and medical management was included in the study.

Results: All 300 patients received intravenous liposomal amphotericin B. 17 patients underwent limited surgical debridement; 137 patients underwent the modified denkers approach for surgical debridement; 146 cases underwent infrastructure maxillectomy. Among them, 18 cases (8%) needed revision surgical debridement within 1 year of follow-up. Only one patient died postoperatively out of 300 patients showing a mortality rate of 0.33%

Conclusion: Early diagnosis of mucormycosis remains difficult and is a significant unmet need, creating a bottleneck in developing novel, efficient clinical interventions. Early surgical debridement along with antifungal helps in reducing mortality greatly.

Keywords:- *Immunosuppression, Liposomal Amphotericin-B, Mucormycosis, CAM.*

I. INTRODUCTION

Despite recent advancements in its identification and treatment, mucormycosis (MCM) remains a deadly condition with a high death rate [4]. It is an angioinvasive infection caused by fungus of the order Mucorales, which includes common fungi like Rhizopus and Mucor [6]. It is an opportunistic infection affecting immunocompromised individuals like DM, hematopoietic malignancy, and post-transplant patients. Increased reporting of invasive mucormycosis post-COVID-19 had been linked to the recent rise in COVID-19 cases in India during the second wave of the pandemic. Numerous case reports and case series depicting mucormycosis in COVID-19 have been published [3]. The number of published articles on mucormycosis increased from 74 in the year 2000 to 786 in the year 2022 according to the search in pubmed [2]. This indicates the disease burden of covid associated mucormycosis(CAM). Before covid era, aspergillosis is the commonest cause of invasive fungal sinusitis. Now the trend changed to mucormycosis with the advent of CAM. Polyenes and triazoles are the medical management of choice for mucor and Surgical debridement is the definitive treatment. Unfortunately, the overall mortality rate for mucormycosis remains 50% despite disfiguring surgical debridement and further antifungal medication, and it nearly reaches 100% among patients with disseminated illness or chronic neutropenia [5].

Most of the cases presented to our hospital had diabetes mellitus and a history of covid 19 as risk factors. They are all treated with antifungals and surgical debridement depending on the general condition.

This study shows the clinical features and outcomes of 300 mucor cases who got treated in GGH, Kurnool.

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II. AIMS AND OBJECTIVES

To reduce the morbidity and mortality rate by timely intervention with both surgical and medical management.

III. MATERIALS AND METHODS

A. Type of study
- It is a prospective study.

B. Source of data
- Department of otorhinolaryngology at Kurnool medical college and Government general hospital, Kurnool, Andhra Pradesh.

C. Period of study
- From June 2021 to August 2022

D.Sample size
- The sample size is 300

E.Method of collection of sample
- Patients of either sex and all ages diagnosed to have mucormycosis and received both surgical and medical management.

F. Inclusion criteria
- Smith and Kirchner criteria

Table 1: Smith and Kirchner criteria

S. No	Location	Characteristics	Presentation
1	Nose	Black necrotic nasal turbinate, Blood in nasal discharge	Unilateral Dried blood clot
2	Orbit	Soft tissue swelling with/without discoloration, induration, and pain	Inflammation around the orbit and nose
3	Upper eyelid	Ptosis	Drooping of the upper eyelid
4	Eyeball	Proptosis	Hooding of eyeball
5	Cranial nerve	Palsy	Multiple unrelated opthalmoplegia

- All cases had expert histopathological confirmation and were culture positive. Samples were most obtained from the sinus cavities.
- Patients who are willing to participate and give informed written consent
- Patients who are fit and underwent surgical management along with medical management

G. Exclusion criteria
- Patients who are COVID-19 positive, have active disease
- patients having noninvasive fungal sinusitis or pathologies other than invasive fungal sinusitis caused by mucor.
- Patients who are not willing to participate and give informed written consent.
- Patients who are not willing to postoperative follow-up.
- Patients who had a psychiatric illness
- Patients who presented with a previous history of surgical debridement (revision cases)

IV. OBSERVATION AND RESULTS

This study comprising 300 patients was conducted in the Department of Otorhinolaryngology at Kurnool medical college and general hospital, Kurnool, Andhra Pradesh.

A. Sex:

Among these 300 patients 173 were male and 127 females. A slight preponderance to males.

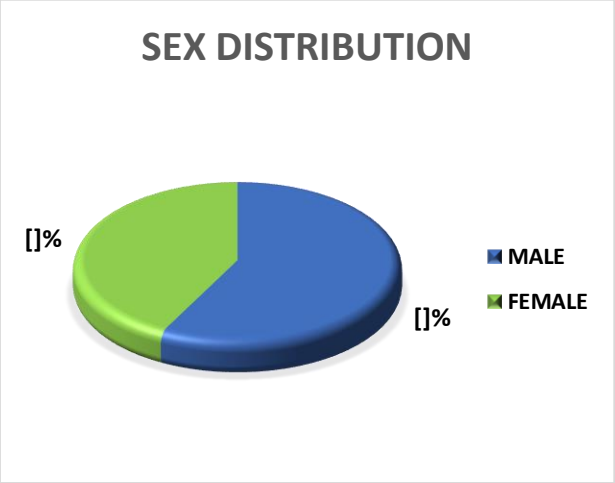

Fig 1: pie chart showing the sex distribution

B. Age:

Among 300 patients 43 patients are between 31-40 yrs.; 129 patients are between 41-50 yrs.; 78 patients are between 51-60 yrs.; 50 patients are between 61-70yrs.

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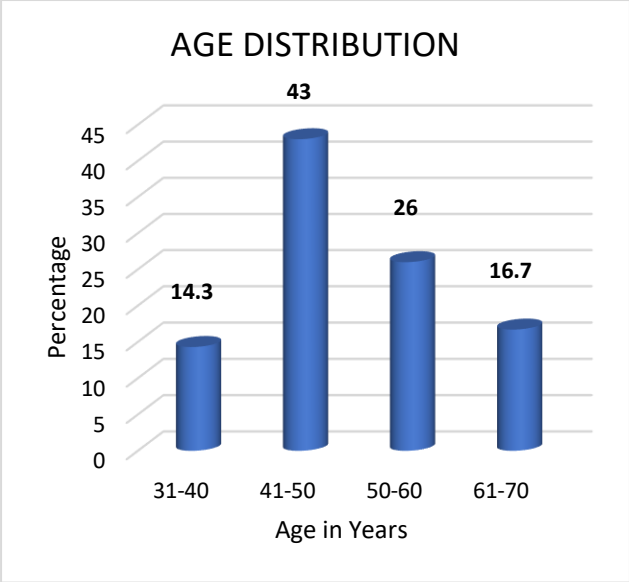

Fig 2: Bar diagram showing the age distribution

C. Geography:

Out of 300 patients, 178 were from rural area and the rest 122 from urban area. 59% of the population belonged to rural and 40% belonged to urban.

D. Risk factors:

Among 300 patients with a previous history of Diabetes mellitus -180; denovo diabetes – 98; CKD- 13; Malignancy-0: Organ transplant-0; Prolonged use of steroids – 107; covid – 258

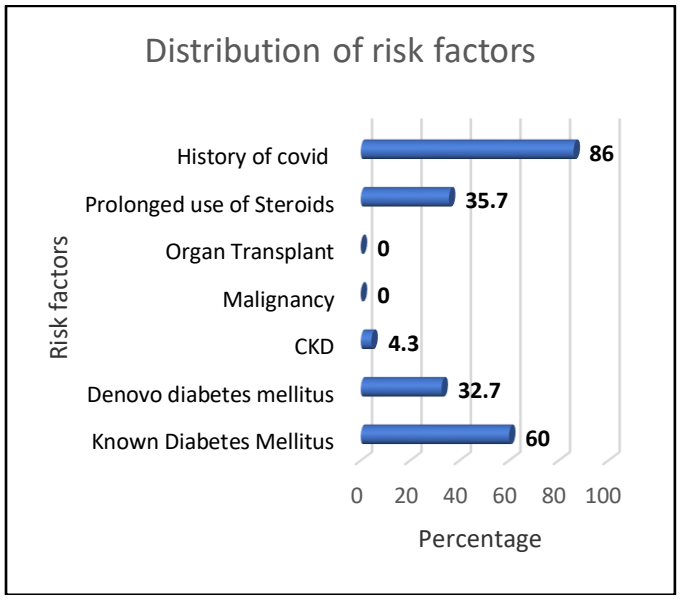

Fig 3: Bar diagram showing the distribution of risk factors

E. Clinical Presentation:

Facial edema and pain were the most common presenting symptoms. Almost all patients had facial pain, swelling, and headache. Patients also complained of nasal discharge, loosening of teeth, swelling, or perforation of the hard palate. Those with orbital involvement had eye pain, conjunctival chemosis, and visual disturbance. Surprisingly many patients presented with only loosening of teeth and gingival pain without any eschar and nasal symptoms. In those cases, intraoperatively only the floor of maxilla involvement is present.

- All of them underwent basic blood investigations and radiological evaluation of MRI PNS T1 and T2 fat-suppressed images and T1 weighted gadolinium contrast images.
- We modified the proposed staging system by Santosh G Honavar [17]. Stage 4 we classified into

✓ Focal meningitis; involvement of cribriform plate; involvement of posterior wall of the sphenoid
✓ Cavernous sinus involvement; diffuse meningitis
✓ Brain infarction; focal brain abscess
✓ Multiple brain abscesses; multiple infarcts

Table 2: Treatment given according to the stages of the patients.

ROCM staging	Number of cases	Surgery done
Stage 1	17	Limited surgical debridement
Stage 2 a, b	71	Modified denkers approach for surgical debridement
Stage 2 c, d	82	Palatal resection and surgical debridement
Stage 3a, b	62	Surgical debridement with or without palatal resection Retrobulbar injection of LAMB
Stage 3 c, d	26	Surgical debridement with or without palatal resection Retrobulbar injection of LAMB or orbital exenteration
Stage 4 a, b	31	Surgical debridement with or without palatal resection Retrobulbar injection of LAMB or orbital exenteration Neurology or neurosurgical intervention
Stage 4 c, d	11	Surgical debridement with or without palatal resection Retrobulbar injection of LAMB or orbital exenteration Neurosurgical intervention

- All 300 patients underwent surgery plus antifungal treatment.
- Out of 300, 17 patients had stage 1 disease; 71 had stage 2a, b; 82 had stage 2c, d; 62 had stage 3a, b; 26 had stage c, d; 31 had stage 4a, b; 11 had stage 4c, d disease.
- All stage 1 patients underwent minimal surgical debridement. In stage 2 disease, 2 a, b (71) and 2 c, d (82) patients underwent a modified denkers approach for surgical debridement and denkers plus palatal resection respectively.
- In stage 3 disease, all patients received a retrobulbar injection of amphotericin B, and orbital exenteration was done in 18 patients along with surgical debridement according to the disease involving the nose.

- Among stage 4 patients, 31 received surgical debridement according to the severity and conservative neurosurgical management except for 11 cases that needed active surgical intervention (craniotomy). Among them, two patients underwent subtotal maxillectomy and orbital exenteration under the same general anesthesia followed by neurosurgical intervention.
- Shortly after surgical debridement, all patients received medical treatment with liposomal amphotericin B at a dosage of 5mg/kg body weight/day. A central line was used to give amphotericin B, and the average course of treatment lasted 11.5 days. 70 participants had infusion-related side effects such as rigidity and chills. Following treatment, 60 patients developed hypokalemia and elevated creatinine levels. 10 patients required switching of amphotericin to posaconazole due side effects. We did not find any instances of disseminated mucormycosis. 3 individuals had concomitant pulmonary mucor when they arrived.
- Out of 300 cases 8% (18) needed revision surgical debridement. One patient died on a postoperative day 3.

V. DISCUSSION

Mucorycosis is a fatal angioinvasive fungal infection. Six types of mucormycosis infection are distinguished by anatomical site involved : (i) rhino-orbital cerebral mucormycosis (ROCM), (ii) pulmonary, (iii) cutaneous, (iv) gastrointestinal, (v) disseminated, and (vi) other forms [9]. All the cases included in our study had ROCM. The inhalation of sporangium is the mode of spread in ROCM. In the presence of hyperglycemia and an acid environment in DKA patients, effective phagocytosis is lost. And also, by utilizing the ketone reductase system of its own and the high levels of free iron in the serum of DKA patients, the fungus grows. During the initial phases of the fungus's spread, infected tissue may seem normal when examined visually during diagnostic nasal endoscopy. Followed by the commencement of an erythematous phase, with or without oedema, and then the infected tissue subsequently develops a violaceous look before a black, necrotic eschar forms as a result of thrombosed blood vessels and tissue infarction [7,8].

Palatal involvement typically results from the direct spread of disease from the maxillary sinus and in the distribution of the sphenopalatine and larger palatine arteries. Oral ulceration is preceded by pain and swelling, and the tissue necrosis that follows can lead to palatal perforation [8]. Typically, infection moves from the ethmoid sinus to the orbit, where it causes proptosis, a loss of extraocular muscle function or total blindness. The infection may spread quickly to nearby tissues including the infratemporal and pterygopalatine fossa.

The sinus mucosa may be thickened on plain radiographs of the paranasal sinuses and orbits, with or without levels of air-fluid, however this is not a definitive sign. Additionally soft tissue oedema, proptosis, and extraocular muscle edoema can be seen[11]. The extent of the disease can be determined by using a magnetic resonance imaging (MRI) or computed tomography (CT) scan with contrast to show bone erosion.

In such cases, a CT of the maxilla and orbit reveal periosteal thickening and bone rupture. MRI and CT scans may be normal in patients with the early rhinocereberal orbital type of mucormycosis but biopsy of probable infection sites should always be carried out in individuals who are thought to be at higher risk. The diagnosis of mucormycosis is only conclusive based on the histological evidence of fungal invasion of the tissues due to the limitations involved with imaging tests [10].

MRI T1 and T2 STIR images and T1 with gadolinium contrast are useful in the diagnosis of mucormycosis compared to CT in our experience. T1 shows fungus as hyperintense and T2 as hyperintense. The contrast shows a black turbinate. Contrast-enhanced MRI can show the disease's perineural spread, while T2-weighted MRI can show intracerebral extension.

Testing for histopathology is always confirmed. Mucor species have a septate hypha with wide angle branching (45°sub to 90°sub). Calcofluor white staining solution was utilised for direct microscopy. The main characteristics of mucoromycetes included enlarged cells (50 μm), thick-walled, refractile hyphae (6-15 μm in diameter), and occasionally distorted hyphae. All resected tissues were sent for HPE for diagnostic confirmation. One thing to keep in mind is that while mucormycosis tends to infiltrate deeply into the tissues, surface swab specimens occasionally can be negative [12].

Although necessary, a cheap culture medium is not currently available. Candidiasis and aspergillosis are differential diagnosis for mucormycosis. Galactomannan and β-D-1,3-glucan are circulating antigens that are positive for invasive aspergillosis, which distinguishes it from mucormycosis [13].

Although Periodic acid-Schiff (PAS) undoubtedly continues to be the gold standard for fungus identification in normal cytological preparations for Candida albicans, AO fluorescence preparations offer a number of advantages in regular cytological smears and for differentiating it from mucormycosis [14].

Based on the following guiding concepts, mucormycosis can be successfully treated.

- Early detection.
- If at all possible, reverse the underlying risk factors (for example, corticosteroids should be administered at reduced dosages or stopped if at all possible and hyperglycemia and acidemia should be corrected in diabetic ketoacidosis).
- Prompt antifungal treatment and urgent surgical debridement of diseased and necrotic tissue.

If mucor is progressing, endoscopic modified Denker surgery is typically necessary. These are the steps:
Step 1: make mucosal incisions
Step 2: Dissection of soft tissues around the maxilla
Step 3: Maxillary bony cuts [15].

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For patients who had palatal involvement, the surgical approach of choice was modified denkers. Postoperatively obturators were used for palatal defects because its cost-effective, and easy for post-operative nasal douching and follow-up.

In this study, young patients with intact palatal mucosa underwent mucoperiosteal flap elevation and bone removal followed by primary closure of the wound by approximating the mucoperiostium. Fortunately, none of them had flap necrosis and the outcome was good.

Amphotericin B is the first-line treatment of choice in the majority of zygomycosis cases, but it is important to monitor serum creatinine, potassium, and magnesium levels as well as blood urea nitrogen (BUN) levels because its use may be connected to side effects like nephrotoxicity (30–50%). Even at greater doses, it is claimed that the other formulation of amphotericin B, liposomal amphotericin B, causes less nephrotoxicity [16].

For the cases that underwent revision surgical debridement, the decision for revision surgery is made based on endoscopic and radiological findings. But picking up the recurrence or residual disease cases remains challenging in early postop. This area needs further research.

A. Diagnostic nasal endoscopy showing necrosed trubinate

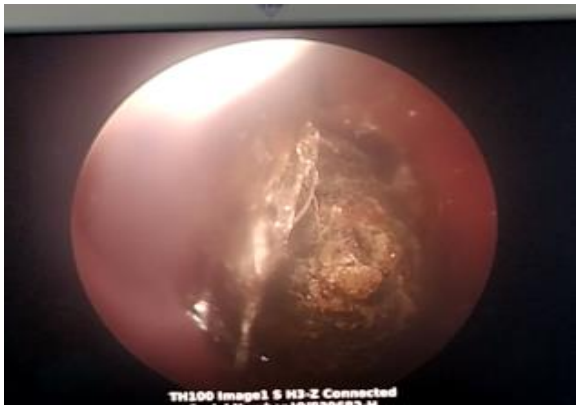

Fig 1:- Diagnostic nasal endoscopy showing necrosed trubinate

B. Intraoperative picture

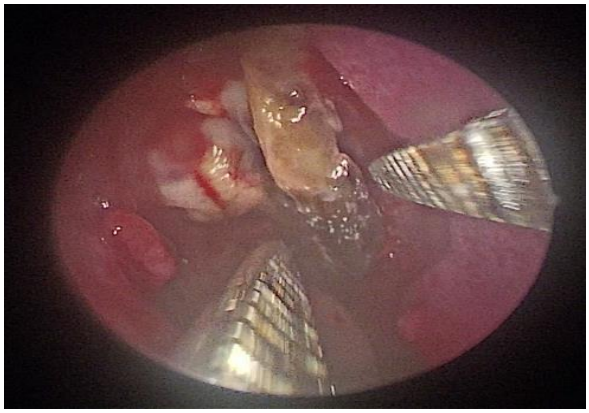

Fig 2 Intraoperative picture

C. Intraoperative picture showing necrosed tissue being removed from medial wall of orbit.

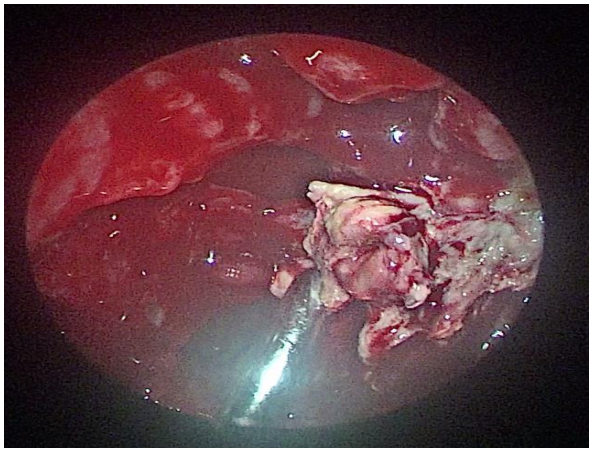

Fig 3 Intraoperative picture showing necrosed tissue being removed from medial wall of orbit.

D. Picture showing ressected maxilla

Fig 4 Picture showing ressected maxilla

VI. CONCLUSION

In conclusion, mucormycosis is an infection that can be lethal and most usually affects people who have compromised immune systems. To lower mortality, management must be started as soon as possible. To start the proper diagnostic workup and treatment, a strong index of suspicion is needed. The rhino-orbital cerebral cavities were involved in our cases most frequently, and DM and COVID-19 were the two predominant underlying diseases. Liposomal amphotericin B can only be used for a short time due to financial constraints, and using an antifungal does not have any life-threatening side effects. From our experience, with effective surgical debridement, 10 to 14 days of antifungal medication was sufficient for recovery. Therefore, early surgical debridement followed by 10-day intravenous antifungal medication produced a positive result. The mortality rate was 0.3%. It demonstrates the value of surgical debridement in lowering fungal loads and enhancing the effectiveness of antifungals.

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CONFLICTS OF INTEREST

We have no conflicts of interest to disclose.

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