Original Article

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Surgery Section

Clinical Presentation and Outcome of Sinonasal Mucormycosis in Pre COVID-19 Era from a Tertiary Care Centre in Uttarakhand: A Cross-sectional Study

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ABSTRACT

Introduction: Sinonasal mucormycosis is an invasive fungal rhinosinusitis which rapidly involves orbits and brain either by direct extension or angioinvasion. Uncontrolled diabetics and immunocompromised patients are prone for this invasive fungal infection. The rapidity of severity of symptoms and morbidity of this invasive fungal infection warrant earliest diagnosis and appropriate management. This research work will be helpful in comparing sinonasal mucormycosis in Coronavirus Disease-2019 (COVID-19) patients as all cases in present study were not associated with COVID-19 infection.

Aim: To observe presenting features and estimate morbidity of mucormycosis patients in tertiary care hospital.

Materials and Methods: This cross-sectional retroprospective study was conducted in Department of Otorhinolaryngology of a tertiary teaching hospital from July 2018 to March 2020. Total 25 sinonasal mucormycosis patients who underwent endoscopic debridement along with amphotericin B were included in this study. Patient was analysed regarding age, gender, chief complains, accompanying co-morbidity, extension of disease, medical treatment, surgical intervention and final outcome. Statistical analysis was done in the form of mean, mode, median and percentage wherever required.

Results: Total 14 (56%) patients were male and 11 (44%) patients were female with median age of 48 years. Total 13 (52 %) patients had facial pain or headache while 13 (52%) had facial or orbital swelling followed by nasal symptoms in 5 (20%), vision loss in 4 (16%) and ptosis in 3 (12%) cases. Twenty four (96%) of cases were having uncontrolled diabetes mellitus. Only 3 (12%) had limited sinonasal disease while 22 (88%) had fungal invasion in orbit. Total 7 (28%) patients had intracranial extension. Out of 25 patients, 4 (16%) expired, 7 (28%) had permanent vision loss and 12 (48%) recovered completely and 2 (8%) left hospital against medical advice.

Conclusion: Present study concluded that mucormycosis is strongly associated with uncontrolled diabetes mellitus. Most common presenting features were facial pain, headache and facial orbital swelling. Only half of the patients recovered with minimal morbidity. Mortality is associated with intracranial extension of mucormycosis. Early diagnosis, extensive and timely endoscopic debridement and appropriate use of amphotericin B is key for treatment of black fungus.

Keywords: Amphotericin B, Black fungus, Coronavirus disease-2019, Diabetes mellitus, Rhinocerebral mucormycosis, Vision loss

INTRODUCTION

Mucormycosis is an invasive fungal infection which may invade to various part of human body including lungs, skin, nose and paranasal sinuses [1]. This potentially fatal opportunistic fungal infection is caused by seven genera of family Mucoraceae [2]. These saprophytic opportunistic pathogens enter in human commonly by inhalation of sporangiospores or occasionally by ingestion or traumatic invasion and attacks immunocompromised individuals by angioinvasion [3]. The prevalence of mucormycosis in India is 70 times more in global comparison with median of two cases per million population [4].

In India, diabetes mellitus is major risk factor for mucormycosis while organ transplantation and malignancies in western developed countries [5]. Prakash H et al., suggested increase in mucormycosis incidence from 12.9 cases per year in 1990-99 to 89 cases in 2013-15 [6]. They also reported that 8-22% case had Diabetic Ketoacidosis (DKA). Rhino-Orbital-Cerebral Mucormycosis (ROCM) is reported as commonest form of mucormycosis seen in 45-74% cases, with 28-54% mortality in sinonasal mucormycosis patients [6].

Sinonasal mucormycosis causes grievous morbidity in form of unrepairable vision loss and high mortality upto 60% in cases of cerebral extension [7]. Early diagnosis, proper antifungal therapy and extensive debridement along with strict control of diabetes is utmost required to improve prognosis [8].

Sinonasal mucormycosis was considered a rare disease in pre COVID-19 time and hence research work is about management of 25 cases of pre COVID sinonasal mucormycosis with emphasis on presentation of symptoms to progression of infection and final prognosis after the course of treatment.

MATERIALS AND METHODS

This cross-sectional retroprospective study was conducted in Department of Otorhinolaryngology of a tertiary teaching hospital after obtaining ethical clearance from Institutional Ethical Committee (IEC) (HIMS/RC/2018/144 dated 26 May 2018) from July 2018 to March 2020. The analysis of the data was done from April 2020 to June 2020.

Inclusion criteria: All the patients diagnosed with sinonasal mucormycosis and who underwent endoscopic debridement were included.

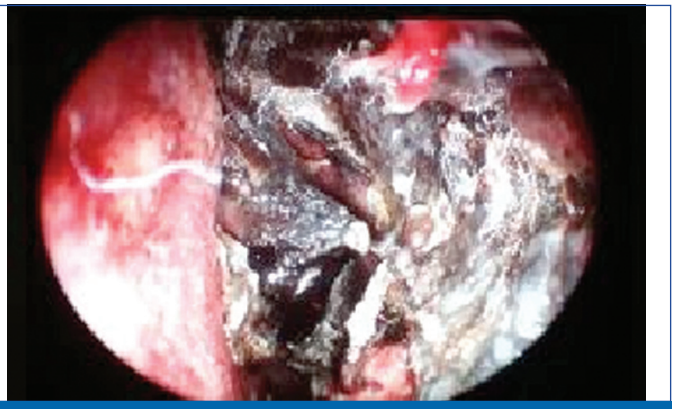
Exclusion criteria: Sinonasal mucormycosis patient who did not undergo endoscopic debridement were excluded.

Sample size calculation: Total 25 patients who were presented in the department within the study period, were enrolled in this study.

Sample size in present study was smaller because mucormycosis was considered as rare disease before COVID-19 pandemic.

Out of 25 patients, data of 15 patients were collected prospectively between July 2018 to March 2020, while 10 patients were added retrospectively between July 2017 to May 2018.

All these patient were diagnosed with mucormycosis before COVID-19 epidemic started. All of the suspected sinonasal mucormycosis patients underwent diagnostic endoscopic evaluation and nasal crusts were sent for KOH mount [9] as first investigation [Table/Fig-1].

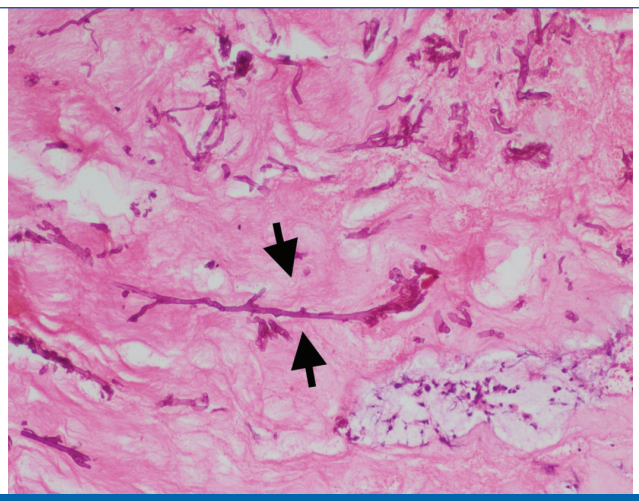


[Table/Fig-1]: Diagnostic nasal endoscopy showing blackish crusts in nasal cavity.

Data were collected regarding age, gender, chief complains, accompanying co-morbidity, extension of disease, medical treatment, surgical intervention and final outcome. Glycosylated HbA1c was done in all patients to look for long term control of diabetes mellitus along with fasting and random blood sugar levels with level more than 6.5% considered as diabetes mellitus [10]. All patients underwent Contrast Enhanced Computerised Tomography (CECT) scan for nose and paranasal sinuses along with orbit cuts. Magnetic Resonance Imaging (MRI) was done in all patients' with intracranial extension on CECT scan and in all patients with vision loss. All patients were evaluated in detail by ophthalmologist for orbital invasion by mucor and assessment of visual acuity before endoscopic surgery.

All were started on amphotericin B as soon as KOH mount report came suggestive of mucormycosis by endocrinologist along with insulin infusion.

Extensive transnasal endoscopic debridement under general anaesthesia was done by Ear, Nose and Throat (ENT) surgeon having minimum five years' experience within 24 hours of positive KOH mount report. The necrotic tissue which was debrided during surgery was sent for histopathological examination in all patients to confirm the diagnosis and exclude other possibilities [Table/Fig-2]. Daily endoscopic evaluation and cleaning was done in postoperative period in endoscopy room till patient showed no crusts in nasal cavity averaging 12 days. All toxicities and medicines related adverse effects were evaluated and treated by endocrinologist.



[Table/Fig-2]: Black arrows showing non septed hyphae in 40X histopathological image with eosine stain.

STATISTICAL ANALYSIS

All data collected using case recording proforma was entered in MS excel 2010 data analysis was performed using Statistical Package for the Social Sciences (SPSS) software version 22.0. Statistical analysis was done in the form of mean, mode and median and percentage wherever required.

RESULTS

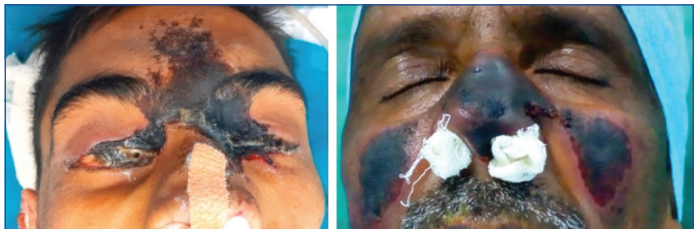
In present study, out of 25 patients, 14 (56%) were male while 11 (44%) were female in age range of 14 years to 75 years with median age 48 years [Table/Fig-3]. The mean age of sinonasal mucormycosis patients was 47.28±5.03 years with 95% confidence level. These all patients were admitted in to ENT department with onset of their symptoms ranging from one day to six months. Out of 25 patients, 5 (20%) admitted within five days of onset of symptoms, 5 (20%) within 6-10 days, 9 (36%) admitted 14-30 days while 6 (24%) were admitted from 45 days to six months of onset of their symptoms. Median admission was 15 days from the onset of symptoms. Out of 25 patients, 13 (52%) had chief complain of swelling either facial or orbital. Total 13 (52%) patients had either headache or facial pain or eye pain as their main complain. Nasal symptoms in the form of nasal obstruction, nose bleed or nasal discharge was present in only 5 (20%) patients. Total 4 (16%) patients presented with complain of vision loss, 3 (12%) with drooping of eye lids, 3 (12%) with fever, 2 (8%) with altered sensorium while one patient each came with complain of hard palate lesion and dysphagia [Table/Fig-4-8]. After clinical examination and battery of tests, 3 (12%) patients were having limited sinonasal mucormycosis, 22 (88%) were having sinonasal and orbital mucormycosis. Out of these 22 patients, 7 (31.8%) were having cerebral extension of mucormycosis. Out of 25 patients 24 (96%) had uncontrolled diabetes mellitus out of which 2 (8%) had type I diabetes mellitus. Total 3 (12%) patients were in DKA while one patient had Type II renal failure. Out of 25 patients one patient did not have diabetes mellitus but was on immunosuppressive medication for six months for rheumatoid arthritis. All 25 patients underwent transnasal endoscopic debridement along with amphotericin B infusion. Two patients underwent orbital decompression, one orbital exenteration, one patient needed right frontal craniotomy and one patient required right partial maxillectomy during the course of treatment. Out of 25 patients, 12 (48%) patients recovered completely, 7 (28%) patients had vision loss, 4 (16%) patients expired and 2 (8%) patients left hospital against medical advice during the course of treatment.

Common CT scan findings were preseptal thickening, opacification of ethmoid sinuses, retroantral fat stranding, medial orbital wall erosion, fat stranding in retrobulbar fat along with bulky and wavy extraocular muscles [Table/Fig-9-12]. The MRI shows hypointensity on T2W imaging in paranasal sinuses. In cases of cavernous sinus thrombosis contrast enhanced MRI T1 W imaging showed non enhancement of cavernous sinus [Table/Fig-13]. Diagnosis was finally confirmed on histopathology by non septate ribbon like hyphae invading blood vessels [Table/Fig-2].

All were started on amphotericin B by endocrinologist along with insulin infusion. Intravenous liposomal amphotericin B was given as 5 mg per kg body weight per day in 300 mL dextrose 5% over 3-4 hours. Intravenous conventional amphotericin B was given as 0.5 mg per kg per day in 500 mL dextrose 5% over 5-6 hours. Amphotericin B was continued till there was no new crusts in nasal cavity. Minimum amphotericin was given for 10 days and maximum for 18 days. Out of these 25 patients a few were started on conventional amphotericin B and other were given either liposomal amphotericin B or lipid emulsion as per availability, toxicity or cost-affordability. Out of these 25 patients, 9 (36%) received lipid emulsion

S. No.	Age (years)	Gender	Presentation	Progression	Co-morbidity	Management	Outcome/Prognosis
1	43	M	Facial pain and swelling 10 d	Sinonasal	Type 2 DM	Endoscopic debridement + Amphotericin B	Recovered
2	64	M	Fever 1 m, Orbital swelling 10 d, vision loss 10 d	Sinonasal + orbital	Type 2 DM	Endoscopic debridement + Amphotericin B +Orbital exenteration	Vision loss
3	50	F	Facial swelling 5 d	Sinonasal + orbital	Type 2 DM	Endoscopic debridement + Amphotericin B	Recovered
4	45	F	Orbital swelling 14 d	Sinonasal + orbital	Type 2 DM	Endoscopic debridement + Amphotericin B +Orbital decompression	Vision loss
5	55	F	Facial pain 15 d	Sinonasal + orbital	Type 2 DM	Endoscopic debridement + Amphotericin B	Recovered
6	50	M	Nasal obstruction 3 m	Sinonasal	Type 2 DM	Endoscopic debridement + Amphotericin B	Recovered
7	45	M	Facial swelling 15 d, facial pain 15 d	Sinonasal + orbital	Type 2 DM	Endoscopic debridement + Amphotericin B + Right Partial Maxillectomy	Recovered
8	40	M	Headache 15 d	Sinonasal + orbital + intrcranial	Type 2 DM	Endoscopic debridement + Amphotericin B	Recovered
9	45	F	Fever 5 d, ptosis 3 d, vision loss 1 d	Sinonasal + orbital + intrcranial	Type 2 DM	Endoscopic debridement + Amphotericin B	Expired
10	14	M	Nasal discharge 6 d, vision loss 4 d	Sinonasal + orbital	Type 1 DM + DKA	Endoscopic debridement + Amphotericin B	LAMA
11	45	F	Facial swelling 7 d, vision loss 2 d	Sinonasal + orbital	Type 2 DM	Endoscopic debridement + Amphotericin B	Vision loss
12	58	F	Facial swelling 5 d	Sinonasal + orbital	Type 2 DM + DKA	Endoscopic debridement + Amphotericin B	Expired
13	56	F	Fever 20 d, orbital swelling 4 d	Sinonasal + orbital + intrcranial	Type 2 DM	Endoscopic debridement + Amphotericin B	Recovered
14	55	M	Orbital swelling 45 d	Sinonasal + orbital	Type 2 DM	Endoscopic debridement + Amphotericin B +Orbital decompression	Recovered
15	56	M	Nose bleed 6 d, headache 6d, orbital swelling 6 d, altered sensorium 2 d	Sinonasal + orbital + intrcranial	Type 2 DM	Endoscopic debridement + Amphotericin B	LAMA
16	42	F	Headache 20 d	Sinonasal + orbital + intrcranial	Rheumatoid arthritis	Endoscopic debridement + Amphotericin B + Right Frontal craniotomy	Recovered
17	23	M	Ptosis 4 d, eye pain 4 d	Sinonasal + orbital	Type 2 DM + Type 2 RF	Endoscopic debridement + Amphotericin B	Expired
18	35	M	Hard palate lesion 6 m	Sinonasal	Type 2 DM +	Endoscopic debridement + Amphotericin B	Recovered
19	48	F	Orbital swelling 45 d, Ptosis 45 d dysphagia 3 d	Sinonasal + orbital + intrcranial	Type 2 DM	Endoscopic debridement + Amphotericin B	Vision loss
20	57	M	Facial pain 2 months	Sinonasal + orbital	Type 2 DM	Endoscopic debridement + Amphotericin B	Recovered
21	47	M	Headache 1 m, Facial swelling 7 d	Sinonasal + orbital	Type 2 DM	Endoscopic debridement + Amphotericin B	Recovered
22	56	F	Eye pain 7 d, headache 5 d, Nose bleed 2 d	Sinonasal + orbital	Type 2 DM	Endoscopic debridement + Amphotericin B	Vision loss
23	75	F	Facial pain + Headache 20 d, Orbital swelling 20 d	Sinonasal + orbital	Type 2 DM	Endoscopic debridement + Amphotericin B + sublabial debridement	Vision loss
24	25	M	Headache 1 d, altered sensorium 8 h	Sinonasal + orbital + intrcranial	Type 1 DM + DKA	Endoscopic debridement + Amphotericin B	Expired
25	53	M	Facial pain 2 m Nasal obstruction 2 m	Sinonasal + orbital	Type 2 DM	Endoscopic debridement + Amphotericin B	Vision loss

[Table/Fig-3]: Characteristics of all 25 mucormycosis patients.
LAMA: Left against medical advice; d: Days; m: Months; h: Hours; DM: Diabetes mellitus; DKA: Diabetic ketoacidosis; RF: Renal failure

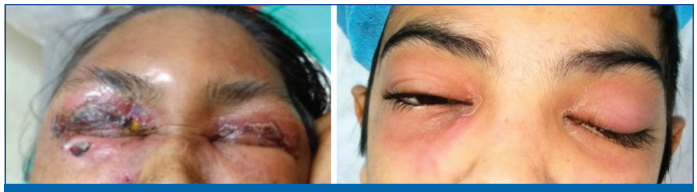


[Table/Fig-4]: Clinical image showing black pigmentation and eye involvement in rhino orbital mucormycosis with intracranial extension; **[Table/Fig-5]:** Clinical image showing black pigmentation over nose and malar region with no eye involvement in sinonasal mucormycosis. (Images from left to right)

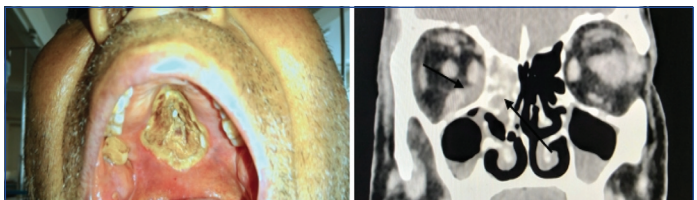
amphotercin B, 7 (28%) received liposomal amphotericin B, 6 (24%) received conventional amphotericin B while 3 (12%) were started on conventional amphotricin B but switched to liposomal amphotericin B due to drug related toxicity.

DISCUSSION

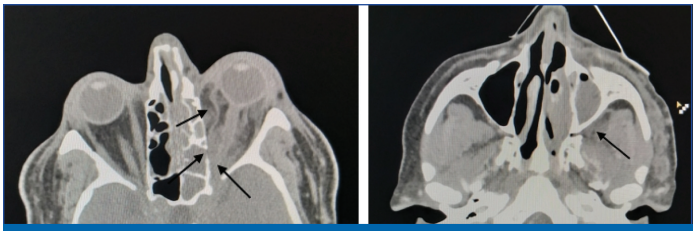
This study was conducted with the aim of analysing presenting complains suggestive of mucormycosis to assessing progression



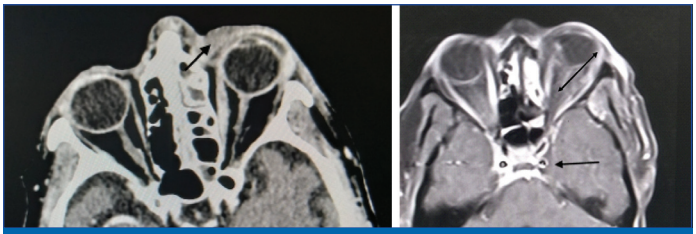
[Table/Fig-6]: Clinical image showing bilateral eye involvement in rhino orbital mucormycosis; **[Table/Fig-7]:** Clinical image showing redness of lids with ptosis in a young mucormycosis patient. (images from left to right)



[Table/Fig-8]: Clinical image showing hard palate crusting with erosion in sinonasal mucormycosis; **[Table/Fig-9]:** CT scan coronal section showing right ethmoid opacification (long black arrow) and soft tissue density in extracoronal compartment right orbit inferomedialy (short black arrow). (images from left to right)



[Table/Fig-10]: CT scan axial section showing fat stranding in left retrobulbar fat (3rd arrow) with wavy medial rectus muscle (1st arrow) with medial orbital wall erosion (2nd arrow); **[Table/Fig-11]:** CT scan axial section showing fat stranding in left retroantral fat (Black arrow). (images from left to right)



[Table/Fig-12]: CT scan axial section showing left preseptal thickening (black arrow); **[Table/Fig-13]:** MRI showing non enhancement of left cavernous sinus suggestive of cavernous sinus thrombosis (single arrow head), Double arrow head showing irregular left eye glove. (images from left to right)

and outcome of mucormycosis in due course of treatment. Out of total 25 patients, 14 (56%) were males while 11 (44%) were females. So incidence of mucormycosis in present study was slightly in favour of male. Median age of patients for mucormycosis was 48 years suggesting condition to be seen commonly in middle age adults. A recent meta-analysis review from 2000-2017 reported that median age for mucormycosis is 51 years and total 63% affected patients were male [11]. Similarly median age for mucormycosis was reported 50.2 years in a retrospective review from India [12]. Comparing to this global meta-analysis and Indian review present study results although comprised less patients, but having similar median age and male preponderance for mucormycosis.

Total 10 (40%) of patients were admitted in tertiary care hospital within 10 days of onset of the symptoms suggesting severity of symptoms pertaining to mucormycosis. Most common symptom was headache or pain either in form of facial pain or eye pain ac-counting in 15 (60%) of the patients. Swellings in form of facial or orbital was one of the presenting feature in 13 (52%) of the patients. Although sinonasal mucormycosis start with nasal cavity, nasal symptoms were trivial and present only in 5 (20%) of the cases. Four patients had vision loss with no perception of light while two patients were in altered sensorium at the time of admission. The patient who came six months after the onset of symptoms had palatal ulcer with fistula opening in nose. Only 3 (12%) of patients had limited sinonasal mucormycosis while 7 (28%) were having rhinocerebral mucormycosis and 15 (60%) had sinonasal mucormycosis with only orbital extension. Jeong W et al., reported 30% sinonasal mucormycosis with orbital involvement and 15% with cerebral involvement [11].

In recent study, infraorbital involvement was quoted in 31% cases and intracranial involvement in 20% cases [13]. This suggests that this invasive fungal infection spreads very rapidly to orbit from sinonasal cavity and within no time it invades brain. Out of 25 patients, 24 (96%) were having uncontrolled diabetes out of which 22 (88%) were having type II diabetes and two patient had type I diabetes. Out of 30 cases of mucormycosis, Nithyanandam S et al., reported uncontrolled diabetes in 88.2% patients [14]. Similarly, 83% patients of mucormycosis had diabetes mellitus in a study from United States [15]. Roden MM et al., 66% sinonasal mucormycosis patient having diabetes mellitus out of whom 43% had cerebral extension [7].

Out of these 24 patients with uncontrolled diabetes mellitus, three developed DKA and one came in renal failure. Only one patient underwent orbital exenteration for preventing spread of invading fungus to brain. Total four patients expired in course of treatment in hospital. Out of 25 patients, 22 (88%) patients had orbital involvement at the presentation to hospital. Out of these 22 patients, 7 (28%) patients also had intracranial extensions. So there were 15 (60%) patients, having orbital invasion but no intracranial invasion. Out of these 15 patients six patients recovered, six patients had vision loss, two expired and one left hospital against the medical advice. All three patients having limited sinonasal disease recovered completely. Out of seven mucormycosis patients who had intracranial extension, three patients recover with minimal morbidity in the form of diminished vision, two expired and one left hospital against the medical advice. Out of four patients who expired two were young male and two were middle age female.

First male who expired, developed type II renal failure while other male had type I diabetes mellitus, developed DKA and rhinocerebral mucormycosis. Out of two female, one developed DKA and other had rhinocerebral mucormycosis. Out of five patients who admitted within five days of their symptoms, 4 (80%) expired and only one recovered. Out of five patients, who admitted from 6 days to 10 days of their symptoms two left hospital against medical advice two had vision loss and one recovered. So out of 10 patients who admitted within 10 days of onset of their symptoms only 2 (20%) patients recovered without morbidity. It suggests that mucormycosis is aggressive and rapidly fatal invasive infection. In two published review, survival in rhinocerebral orbital mucormycosis was reported 59.5% and 60% only [16,17]. Prakash H et al., reported 46.7% mortality out of 388 cases of mucormycosis [6]. In a study by Saravanan PK et al., inhospital mortality was reported only 13% out of 39% cases [13]. Petrikkos G et al., concluded that severity of symptoms, degree of immunosuppression and prompt surgical treatment as most important factors for outcome in mucormycosis patients [18]. Patel A et al., concluded intracranial extension, shorter duration of symptoms and antifungal therapy and conventional amphotericin B as independent risk factors of mortality [19]. In present study, out of 12 patients who recovered completely, 9 (75%) received either lipid emulsion or liposomal amphotericin B, while 3 (25%) received conventional amphotericin B. Out of four patients who expired 3 (75%) received either lipid emulsion or liposomal amphotericin B, while 1 (25%) received conventional amphotericin B. All seven patients who recovered with vision loss as morbidity receive either lipid emulsion or liposomal amphotericin B. The two patients who left against medical advice were started on conventional amphotericin B. Stone NR et al., suggested that liposomal amphotercin B have less nephrotoxicity, better tissue and Central Nervous System (CNS) penetration and prolonged mean residence time in tissue [20].

Behaviour of mucormycosis is different in individuals as even these patients reached tertiary care hospital very early but morbidity and mortality could not be prevented by far. Out of 15 patients who presented from 14th day to 6 months of onset of symptoms total 5 (33%) had vision loss while 10 (66%) recovered with minimal morbidity suggesting acuity and severity of symptoms is directly related to morbidity and mortality in mucormycosis. The severity of the patient's underlying condition, the degree of immunosuppression, and prompt surgical treatment are the most important factors contributing to the outcome.

Limitation(s)

First limitation of this study was small sample size as sinonasal mucormycosis was considered rare disease in pre COVID-19 time, Second limitation was that all patients were not enrolled prospectively and all patients not received similar type of amphotericin due to different reasons.

CONCLUSION(S)

A 96% of the mucormycosis patient had uncontrolled diabetes mellitus as associated co-morbidity. Most common complaints were facial pain, headache and orbitalfacial swelling. Limited sinonasal pathology was seldom seen, while fungal invasion to orbit

was a norm. Only upto 50% patients recover with minimal morbidity in mucormycosis. Extensive timely endoscopic debridement, appropriate type and dose of amphotericin B along with strict control over co-morbidity is key in the successful management of mucormycosis. The sensitisation of physician and endocrinologist about warning clinical features of mucormycosis is essential for early diagnosis and timely management.

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