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## Diagnosis and clinical outcomes for Rhino-Cerebral/ Orbital Mucormycosis: An experience sharing

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### Abstract

**Aim:** Rhino-Orbito-Cerebral Mucormycosis (ROCM) is an invasive fungal infection. An under diagnosed and underreported disease in India, it is rapidly fatal without an early diagnosis and treatment. We report the survival rate in our hospital, significant association with sinus involvement and therapy

**Methods:** The clinical and laboratory data collected retrospectively from patients with a diagnosis of invasive zygomycosis, over a four and half year period (January 2015-July 2019) were combined and analysed from medical records. We analyzed clinical features, results of laboratory and radiological examinations, nasal endoscopy, treatment management outcomes of all cases.

**Results:** A total of sixteen cases of invasive ROCM were diagnosed and treated at St Stephens Hospital, Delhi, from January 2015 to July 2019 of which ten were males (62.5%). All were diabetic (100%), DKA (Diabetic Keto Acidosis) and renal impairment was seen in 11 (68.75%) patients. All were given L-Amphotericin B (100%). Thirteen (81.2%) cases underwent surgical procedure. Duration of treatment with L-Amphotericin was significantly associated with improved outcomes ( $p=0.03$ ). Maxillary and ethmoid sinus involvement was significantly associated with improved outcomes ( $p=0.02$ ). Diagnosis was based on direct microscopic findings, mycology culture and histopathology findings (EORTC/MSG Consensus Group). Survival rate was 57.25% (9 improved and 7 expired).

**Conclusion:** Duration of treatment with L Amphotericin and maxillary sinus involvement were associated with improved outcomes. In an otherwise lethal disease, rapid administration of Amphotericin B with surgery can go a long way in improving the survival rate in proven/probable mucormycosis.

**Keywords:** Rhino-Orbito-Cerebral Mucormycosis; L amphotericin; survival rate; DKA.

## Introduction

The zygomycoses are infections caused by class Zygomycetes, order Mucorales. Its various clinical manifestations are Rhino-Orbital-Cerebral Mucormycosis (ROCM), cutaneous, pulmonary, cerebral zygomycosis. It is a fulminant fungal infection associated with high morbidity and mortality rates [1,2]. In the US, the incidence was estimated to be 1.7 cases per million people per year, as per one population-based study. Jeong et al in their review put forth burden is higher in Europe than in Asia, as they reported 34% in Europe, followed by Asia (31%) and North or South America (28%), Africa (3%) etc. whereas Chakraborty et al recently published that India has a higher prevalence and incidence, but is highly underreported [3,4].

Lichtheimia, Mucor, Rhizomucor, Saksenaea, Apophysomyces, and Cunninghamella are commonly isolated fungi in Zygomycotic infections. These are angio-invasive causing vessel thrombosis and tissue necrosis along with the tendency to disseminate. Rhino-Orbital-Cerebral Mucormycosis (ROCM) may be rapidly fatal if not recognized early and treated promptly. Survival rate varies from 3% in untreated cases to 70% in those treated with both surgery and antifungal therapy [1].

It has been documented that zygomycotic infections have been increasing by the passing decades, with as low as 0% in 1940s, to as high as 70% in the 1980s [1]. Diabetes mellitus is an independent risk factor for mucormycosis in 36%-88% of cases, particularly those with ketoacidosis [5]. Studies on poor prognostic factors for mucormycosis are being published but factors for survival outcomes still need enough studies. Similarly, the significance of rapid diagnosis is well known, but had not been identified in a statistical way. In this study, we have depicted the involvement of various sinuses and its effects on patient outcome. The present study showcases the factors for improved survival outcomes of patients with ROCM infection. An attempt has been made to analyze clinical features, predisposing factors and clinical outcomes.

Under reporting of mucormycosis in Asian countries, especially India, leads to faulty statistics.

We attempt to bring across the mucormycosis cases treated in our set up in North India and discuss the factors leading to better patient outcome.

## Methods

Sixteen ROCM patients initially presenting to our hospital between January 2015 and July 2019 (4 and half years duration) were investigated. Patients were evaluated at the time of presentation with a detailed history, systemic examination, ENT, ophthalmic, and neurological examination to assess the extent of disease, nasal endoscopy with biopsy, and results of laboratory and radiological examinations.

## Definition

According to the criteria put forth by the European Organization for the Research and Treatment of Cancer/Mycoses Study Group (EORTC/MSG) for Invasive Fungal Disease (IFD), [6] patients with mycological and histo-pathological evidence of mucormycosis in tissue biopsy (including observation of aseptate hyphae branching at wide angle and ribbon-like hyphae asso-

ciated with tissue damage) taken by Functional Endoscopy Sinus Surgery (FESS) or needle aspiration were considered in the study as a proven case.

The diagnosis of mucormycosis was made initially by screening for aseptate hyphae by 10% KOH, which was later confirmed by mycology culture. Histopathology examination of biopsy samples reported extensive necrosis and infiltration by broad, aseptate fungal hyphae branching at right angle. Treatment was promptly started irrespective of proven/ probable status of mucormycosis.

All clinical characteristics – clinical signs & symptoms including ophthalmic, endocrine and neurologic findings, co-morbid conditions, medical and surgical interventions and clinical outcomes were recorded and analyzed in specific data sheets.

## Statistical analysis

All variables were expressed as means with SD, unless otherwise indicated. Categorical variables were compared by Chi square analysis and continuous variables with normal distributions were compared using Student's test. All statistical tests were performed using SPSS Software for Windows, trial version 20.0 (IBM, Armonk, NY, USA). P-value < 0.05 was considered to be statistically significant.

## Results

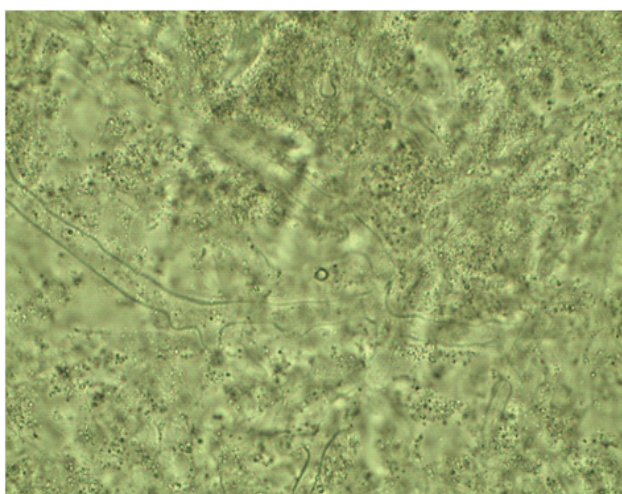
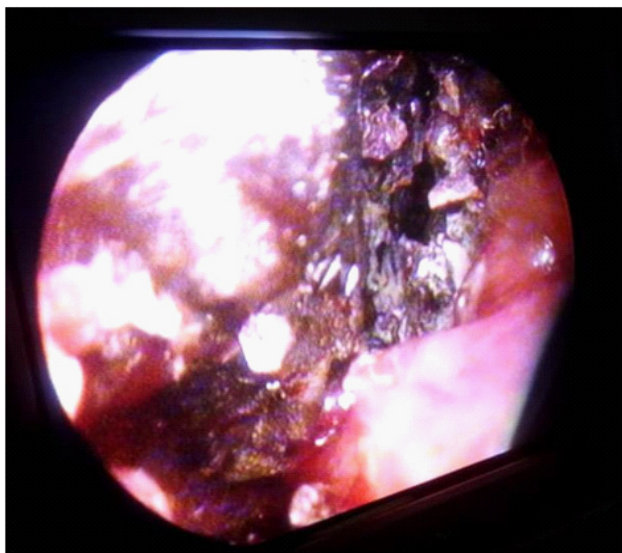
Sixteen cases of Rhino-orbital-cerebral mucormycosis were diagnosed and treated in SSH between January 2015 to July 2019 (four and half years). The demographic characteristics, co-morbid conditions, clinical signs & symptoms, medical and surgical treatment, and clinical outcomes are presented in Table 1.

Of these 6 (37.5%) cases were females and 10 (62.5%) were males. Mean age was 49.75 years (14-75 years). In the present study, all patients had DM (100%) whereas 11 (68.7%) were in ketoacidosis and 5 cases (31.2%) had uncontrolled DM during presentation. Peri-orbital edema (83.4%) and facial swelling (75%) were seen in 83.4% and 75% of cases respectively. Recurrent fungal sinusitis was seen in 18.5% of cases and concomitant herpes infection seen in 12.5% of cases (Table 1). Pansinusitis was seen in 7 cases (43.75%), 3 patients had orbital cellulitis (CASES NO.3,6,15) and 1 glaucoma (6.2%). Two cases (12.5%) had h/o surgery prior to onset of symptoms.

CT/MRI scan of the paranasal sinuses, orbit and craniocerebrum was done for nine cases (56.2%). Two cases (12.5%) presented with cavernous sinuses thrombosis (Table 1).

The fungal culture was done for thirteen of sixteen cases (13/16, 81.7%), Zygomycetes like, Rhizopus, Mucor, Absidia were isolated. Thus a culture based diagnosis of mucormycosis was made (Table 1). The histological examination was positive in twelve cases (75%). Thirteen cases (81.7%) had proven mucormycosis and 3 (18.2%) were probable mucormycosis according to EORTC definition.

Medical and surgical treatment was given to 13 cases (81.7%), whereas 3 cases (18.2%) were given only medical treatment. Of the 16 patients treated, 9 improved and 7 expired (43.75% mortality at discharge). Table 2 shows risk factors associated with survival in patients with invasive mucormycosis infection.



**Figure 1:** (Above): Functional endoscopic sinus surgery (fess) showing black necrotic tissue surrounded by normal tissue. (Below): Broad, aseptate, hyaline, branching hyphae from direct tissue specimen.

On bivariate analysis, the factors identified as significantly associated with outcomes for patients with ROCM were duration of administering L-Amphotericin ( $p=0.03$ ), Maxillary and ethmoid sinuses were involved with improved survival outcomes, independently as well as together. (maxillary  $p=0.02$ ; ethmoid  $p=0.06$ , Table 1). Days of stay in hospital showed trend towards survival outcomes for patients with mucormycosis, though these did not reach statistical significances but were close ( $P = 0.06$ ).

### Discussion

Mucormycosis is a rare filamentous and fatal fungal infection mostly encountered among immuno-suppressed patients. The hallmark of mucormycosis is angioinvasion resulting in vessel thrombosis and tissue infarction/necrosis extensively. Various studies report its predilection for different anatomical sites such as- rhino-orbito-cerebral (44-49%), followed by cutaneous (10-16%), pulmonary (10-11%), disseminated (6-11.6%) and gastrointestinal (2-11%) presentations [5,7].

Improved outcomes were seen with age, although this did not achieve the statistical significance ( $p=0.08$ ).

Rhinocerebral mucormycosis (ROCM) is the most common form of mucormycosis in patients with diabetes mellitus

[5] and diabetic ketoacidosis increases the predisposition to ROCM [12]. In the present study, diabetic ketoacidosis and renal impairment were seen in eleven patients each, respectively. (11/16; 68.75%). A study from Iran published 86.7% cases with DM whereas another study reported 74% cases [11-13]. Role of DM has been published enough. All patients had DM, of which 4 patients (25%) were diagnosed with diabetes on admission similar to that probated by Charaborty et al., who attributed mucormycosis as a diabetes-defining illness in 23%-43% of patients with no regular health check-up. Estimated diabetic population of India was 61.3 million in 2011 and it is estimated to reach 101.2 million in 2030 thus widening the propensity of mucormycosis [4,10]. Roden et al. reported renal failure and diabetes to be an independent risk factors for mortality on multivariate regression analysis [1]. We achieved no statistical significance in these parameters (Table 1)( $p =0.6$ ,  $p=0.2$  respectively). The interplay of hyperglycemia and low pH in patients with DKA causes phagocytic dysfunction whereby there is impaired chemotaxis and defective intracellular killing by both oxidative and non-oxidative mechanisms [1,4].

The initial symptoms include eye or facial pain and facial numbness, altered sensorium, followed by the onset of conjunctival suffusion, blurry vision, and soft tissue swelling. In the present study, peri- orbital edema and facial swelling were the most common signs (68.75% and 68.75% respectively, Table 2) which is in line with that reported by Abdollahiet al [7] whereas Jiang et al from China reported decrease in vision and involvement of cranial nerves as the most common signs (100%) [11].

The significance of rapid diagnosis is well known, but had not been identified in a statistical way. In this study, we have depicted the involvement of various sinuses and its effects on patient outcome. Also, the present study showcases the effect of duration of treatment and stay in hospital on improved outcomes of patients with ROCM infection.

**Involvement of sinuses:** Maxillary and ethmoid sinuses were involved with improved outcomes, independently as well as together (Maxillary  $p=0.02$ ; ethmoid  $p=0.006$ ; Table 2). Maxillary sinus was the most commonly involved 12 (75%), followed by ethmoid sinus 11 (68.75%), in contrast to that observed by Jiang et al (27.27% 3/11) [11]. Frontal and sphenoid sinuses were equally involved in 9 cases (44.37%). Pansinusitis was seen in 43.75% patients (7/16) in the present study which is comparable to that observed by Maureen et al (39%) [1] (Table 1) but lower as compared to that seen by Jiang et al [11] (72.72%). Cavernous sinus thrombosis was seen in 2 patients (2/16-12.5%) as compared to another study from China (4/11= 36.6%) [11]. Ubiquitous nature in the environment provides entry of fungal spores into the nasopharyngeal tract causing the disease to commonly start in the nasal mucosa turbinate or palate. This further spreads to the paranasal sinuses. Another mode of invasion is through cribriform plate and roof of the orbit, as they

**Table 2:** Sinus involvement in ROCM.

Characteristics	Total	Improved	Expired	*p-value
Maxillary	12	8	4	0.02
Ethmoid	11	9	2	0.006
Sphenoid	9	5	4	0.4
Frontal	9	5	4	0.2
Maxillary+ Ethmoid	12	8	4	0.02



**Table 3:** Factors related to the patient outcome on univariate analysis.

Indicators	N= 16	Improved	Expired	P value (<0.05 significant)
Age	16	9	7	0.08
Gender	Male 9 Female 7	6 3	3 4	0.3
Patients in DKA	11	6	5	0.6
Deranged renal function	11 (68.75%)	5 (31.25)	6 (37.5%)	0.2
Interval from patient admission to diagnosis-(KOH)	29.43 h(471/16)	30 h(1.25 days)	201/7 h =28.71hrs	0.9
Time ONSET OF to medical Rx from symptom onset	12.81 (205/16)	15.11 (136/9)	69/7=9.8	0.3
Time to MEDICAL TREATMENT (from admission)	2(32/16)	2.5 DAYS (23/9)	9/7 (1.2)days	0.17
Days of Surgery from onset of symptom	11.4 (183/16)	1198 (14.87)	54/5 (10.8)	0.4
Days of Surgery (from day of admission)	3.5 (32/9)	2.3 (19/8 )	1.2 (6/5)	0.2
Duration of treatment L AMB	8.68(139/16)	11 days	5.71	0.03
Stay in hospital	9.9 days (158/16)	12.66 days (114/9)	44/7=6.2	0.06

are anatomically very thin, therefore eventually complicating as rhino-orbito-cerebral form [14].

13 cases were culture positive, histopathology positive or both and thus categorized as proven mucormycosis. 3 patients were categorized as Probable mucormycosis since microscopy was positive, 1 patient was culture positive but histopathology negative, the other was histopathology positive and culture negative and in 3rd case patient refused the tests but was admitted in ICU (ICU patient diagnosed as probable mucormycosis in accordance with EORTC guidelines) [6]. Thirteen proven mucormycosis, fungal culture was positive in 12 cases. Histopathology was done for 13 cases of which, 11 were positive and 2 were negative. Fungal culture was done for 15 cases (15/16).

A positive fungal culture report was seen in 75% (12/16) cases in the present study, with *Rhizopus* being the most common isolate (75%), followed by *Mucor* (16.67%) and *Absidia* (8.3%). 50% positive cultures were observed by Maureen et al [1] and only 33.3% were ascribed by another author. 7 Another study reported confirmation by both histopathology and fungal culture in 8 cases (44%) and among 172 cases with cultures, *Rhizopus* spp. (34%), *Mucor* spp. (19%) and *Lichtheimia* (formerly *Absidia*) spp. (19%) were most commonly identified [9]. A meta-analysis of mucormycosis cases revealed that *Rhizopus* species was often associated with ROCM form of the disease [9].

Probability value was calculated for certain characteristics (Table 3).

Duration of L-Amb- Antifungal therapy was started promptly for all patients immediately after receiving KOH screening report. Duration of giving L-Amphotericin has significant p value in terms of outcomes (p=0.03). This is supported by observation that those who expired had treatment cut short (Table 3).

**Duration of stay:** Calculated from time of admission to discharge. Duration of stay has been shown to be associated with positive survival outcomes, although in the present study significance was not reached (p= 0.06) [4]. Average stay in hospital, for all patients, was 9 days (145/16= 9.06), ranging from 3 to 23 days.

**Interval from patient admission to diagnosis** calculated as duration between admissions of patient to the time when sample was sent for KOH test. Average time for sending specimen for KOH screening test was 2 days. Although not statistically significant in this study, early diagnosis led to early initiation of treatment whether surgical, medical or both (Table 1).

Medical treatment was started promptly on receiving the screening report with DM and acute onset nasal symptoms. Survival outcomes deteriorate if medical treatment is delayed. Of those expired (7), 2 had been diagnosed as cases of mucormycosis (cases 7,15) and one patient was already given liposomal Amphotericin for 30 days before coming to the present hospital (case 15) (Table 1). Four were referred cases from other hospitals, which showcases delay in diagnosis or diagnostic dilemma.

Thirteen patients were treated both surgically and medically with antifungal therapy whereas antifungal chemotherapy alone was given to 3 patients. Maureen et al observed survival was 61% (324 of 532) for cases treated medically with amphotericin B deoxycholate and 57% (51 of 90) for cases treated with surgery alone, whereas survival was 70% (328 of 470) for cases treated with antifungal therapy and surgery [1]. Only 3% (8 of 241 patients) of cases, who were not treated at all, survived. Our data was limited so as to make such observations. They also documented the overall mortality to be 54% and rhinocerebral and localized cerebral infection were associated with a mortality of 62%, 1 as compared to the present data which encompasses only rhinocerebral forms (mortality 43.75%, Table 4). Skaida et al [12] reported 4% (10/230) of all cases were diagnosed post-mortem (by histology and culture), while 6% (14/230) were diagnosed during the last 24 h before death leading to delay/inability to start antifungal treatment [12].

A study found that delaying AmB-based therapy by initiating treatment  $\geq 6$  days after diagnosis resulted in a two fold increase in mortality rate at 12 weeks after diagnosis, compared with early treatment (82.9% vs 48.6%) [3,4]. In the present study, all cases were diagnosed antemortem. Another series by Pagano et al reported 54% of cases were, diagnosed of zygomycosis ante-mortem [12]. Same authors reported that thirty-three patients received no treatment, either because the diagnosis was

made post-mortem (in 10), or during the last 24 h prior to death (in 14), or because only surgical treatment was performed (in 9)12It was shown that even 12 hours delay in diagnosis could be fatal and studies on autopsy reported that 50% of diagnoses were postmortem [1].

Survival rate was 57.25% in the present study. Rapid progressive nature of ROCM along with marked increase in the mortality rate once the fungus penetrates the cerebral tissue advocates for proper evaluation of any diabetic patient with complaints of headache or decreased vision or nasal discharge to rule out mucormycosis. Infection can sometimes extend from the sinuses into the mouth and produce painful, necrotic ulcerations of the hard palate [1]. Fungal invasion extending to the cranium thereby furthering the infarction, might be the reason for 7 of 16 patients (43.75%) who died in the present study (Table 4).

**Table 4:** Mortality data of Mucormycosis (overall) from various studies.

Study	Total mortality
Thomas [13]	47%
Present study	43.75%
Maureen M [1]	54%
Lucei [14]	65.90%
Nin iang [11]	83%
George petroff [5]	88%
A. Chakraborty [4]	45%

Rapidity of diagnosis, reversal of the underlying predisposing factors (if possible), and appropriate surgical and medical therapy limit the progression of necrosis. Firstly early diagnosis can lead to early excision of necrosed tissue, thereby enabling better penetration of antifungal drugs. Secondly, localized lesions can be removed which decreases the chances of dissemination of fungi to other critical areas. Surgical debridement diminishes the fungal and necrotic burden and prevents further local spread to adjacent sinuses and orbit. Surgical debridement along with intranasal douching of Liposomal Amphotericin B further prevents and controls spread of the fungi, although there is a dearth of evidence in this regard.

### Conclusion

Mucormycosis is an emerging infection with severe consequences, if not diagnosed and treated promptly. Burden of the disease, in India and the world, is incomprehensible due to lack of statistics. Awareness of clinicians, cooperation amongst clinicians, mycologists and pathologists to discuss, diagnose as well as report at the earliest leading to prompt initiation of the therapy. Treatment with Liposomal Amphotericin B with surgery improves survival outcomes of patients with ROCM.

### Declarations

#### Authorship policy

- Conceived of or designed study- Dr Yukti Sharma, Dr SK Chumber.
- Performed research- Dr Yukti Sharma, Dr John Punnose, Dr SK Chumber, Dr Susan K Sabastian, Dr Molly Joseph.
- Analyzed data- Dr Kapil Goel.

- Contributed new methods or models- Dr Susan K Sebastian, Dr SK Chumber, Dr John Punnose.

- Wrote the paper"- Dr Yukti Sharma.

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**Declarations (ethics):** Approved by Ethics Committee St Stephen's Hospital, no. SSHEC/R0180.

**Conflict of interest / Competing interests:** Authors have no conflict of interest.

**Ethics approval:** No. SSHEC/R0180.

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