



## IS MUCOR A ONE WAY TICKET IN DIABETES MELLITUS???? – A PROSPECTIVE STUDY

### Otolaryngology

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### ABSTRACT

**Summary** – Mucormycosis was considered universally fatal until isolation of Amphotericin B in 1961, the 1<sup>st</sup> survivor was reported. Having a prevalence rate of around 8% - 13% of all fungal infections, these cause fatal infections in immune-compromised individuals. Being the diabetic capital, most of the cases present at advanced stage, commonly rhinocerebral or rhino-orbito-cerebral types. Here, we present a case series of mucormycosis, their clinical management, and course of the disease with literature review and suggest an easy protocol.

**Objective** – Devise a treatment protocol to help in early diagnosis of mucormycosis.

**Methods** – Prospective, cross-sectional, interventional study. Duration – 6 months. N=13 consecutive mucormycosis cases. Demographic parameters, co-morbidities, clinical presentation, stage at presentation, diagnostic nasal endoscopy findings, radio-imaging, and Quality-Of-Life (QOL) questionnaire data were recorded and compared. Statistical analyses were done.

**Results** – Mucorales were commonly isolated from diabetic individuals. High mortality rate. Poor QOL.

### KEYWORDS

Mucormycosis, Diagnostic nasal endoscopy, Liposomal Amphotericin B, Rhinocerebral,

### Introduction:

Fungi of the order Mucorales often cause devastating invasive fungal infections, primarily in patients with risk factors, especially diabetes mellitus type 2 which is a common co-morbidity in Indian population.<sup>[1]</sup> Prevalence of mucormycosis infection is from 8.3% - 13% of documented fungal infections.<sup>[2]</sup> The annual incidence values from Indian population is around 12.9%.<sup>[3]</sup> This goes up steeply in case of diabetics. Common route of entry into the human body is by respiratory tract, eliciting an acute allergic response due to foreign protein entry.<sup>[4]</sup> Morbidity due to mucormycosis occurs due to extensive vessel thrombosis and ischemic tissue necrosis while mortality is attributed to rapid progression and intracranial extension even after active management.<sup>[5]</sup> The principal risk factors implicated in mucormycosis include uncontrolled diabetes and diabetic ketoacidosis.<sup>[6]</sup>

Rhino-Orbito-Cerebral Mucormycosis (ROCM) type, being the commonest form<sup>[5]</sup>, causes a very high residual morbidity and mortality due to the angio-invasive property of the fungus. Histopathology is characterized by the presence of broad aseptate filamentous fungi branching at right angles.<sup>[5]</sup> Impaired delivery of the antifungal drugs to the site of infection because of vascular thrombosis and limited aggressive surgery because of the complex anatomy of the rhino-orbital region cautions for early diagnosis and aggressive management in these patients. Diabetic patients with ROCM have the best chance of survival, as the underlying metabolic derangement is most amenable to treatment.<sup>[7]</sup>

### Need for the study:

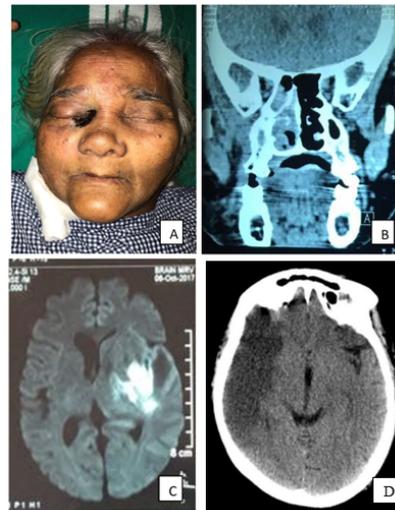
In diabetic patients with mucormycosis,

1. Assess importance of early Diagnostic Nasal Endoscopy
2. Assess Quality-of-life measures
3. Devise management protocol for better outcomes

### Case series description:

16 consecutive middle-aged patients with uncontrolled diabetes mellitus type 2, were referred from the department of Internal medicine to Otorhinolaryngology out-patient department (OPD) for opinion regarding development of various ear, nose, throat (ENT) and head & neck presentations (**Fig. 1**). Despite being on both oral and injectable hypoglycemic agents, their glycemic control was not achieved. A few patients had history of tooth extraction, habits like

tobacco chewing, smoking and alcohol intake, and co-morbidities like systemic hypertension. They were on irregular treatment as some had crossed-over to homeopathic or native treatment prescribed elsewhere – the treatment details were not available. The complications noticed in the patients were epistaxis, proptosis, single / multiple cranial nerve palsies, ophthalmoplegia and hemifacial cellulitis. Medically, they were complicating with ketoacidosis, renal failure and ascites.



**Figure 1A** – Eschar Right media canthus. **1B** – Computed Tomography of Paranasal Sinus showing invasive fungal sinusitis involving the ethmoids. **1C** – Magnetic Resonance imaging Brain – Intracranial extension with midline shift. **1D** – Computed Tomography of brain – Right middle cerebral artery infarct.

### Materials and methods:

Prospective, cross-sectional study. N = 16 (consecutive cases – convenient sampling – single blinding). Duration: 6 months (February 2017 – August 2017). Institutional Review Board / Ethics committee clearance was obtained. Written Informed consent was obtained from the patients and their attenders. Proforma – demographic data and

clinical parameters documented and compared. Necessary specialties like Nephrology, Internal Medicine, Cardiology, Neurology and Radiology were consulted – treated as advised. All patients underwent diagnostic nasal endoscopy (DNE) and radio-diagnostics followed by emergent Endoscopic Surgical debridement to reduce the fungal load both locally and systemically. Histopathology and fungal staining / culture samples collected. Medically they were treated with Liposomal Amphotericin B by slow intravenous (IV) infusion and normal saline nasal douching. Alternate day renal function tests were done and doses titrated accordingly. All patients received Liposomal Amphotericin at a dosage of 0.5 – 0.7 mg/kg/day, getting a total dose of 1 – 1.5 gm.

IBM SPSS v22 for Windows (SPSS Inc., Chicago, Illinois) was the statistical tool used for computing values. Categorical data and continuous data were represented as number (percent) and mean ( $\pm$  standard deviation) respectively. Health Utility Index-3 (HUI-3)<sup>[8]</sup> was the tool used to assess health-related Quality-of-life (HrQoL); filled either by the patient or proxy-filled by attenders, if the patient's condition did not allow for manual completion. If mortality was expected, the patient's final values would be downgraded automatically as expecting care-takers to complete may prove to be insensitive. Paired t-test was used to check difference between mean pre-treatment and post-treatment values of study candidates. Odds ratio was computed to check association.  $p < 0.05$  was considered statistically significant.

**Inclusion Criteria**

1. Age > 20 years
2. Diabetes mellitus type 2
3. Necrotic tissue on diagnostic nasal endoscopy (Fig. 2)

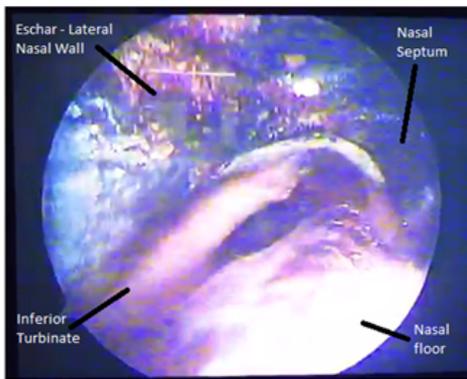


Figure 2. Diagnostic Nasal Endoscopy - Eschar involving lateral nasal wall with septum and floor

4. Invasive fungal sinusitis

**Exclusion Criteria**

1. Age < 20 years
2. Non-diabetic
3. DNE – normal mucosa
4. Allergic fungal sinusitis

**Observation and Results:**

Demographic data – Table 1.

Characteristics	Data
Female	11 (84.62)*
Age (years)	47.77 (4.003)**
Height (cms)	167.77 (26.87)**
Weight (kgs)	89.73 (14.33)**
Body-Mass Index (BMI, kg/m <sup>2</sup> )	31.9 (0.87)**
Diabetes Mellitus Type 2	12 (92.31)*
Systemic Hypertension	8 (61.54)*
Dental Extraction	4 (30.77)*
HbA1c	7.7 (1.24)**
Fasting Blood Sugar (FBS)	249.62 (77.27)**
Post-Prandial Blood Sugar (PPBS)	377.08 (127.4)**

Clinical parameters noted from the cohort. (Fig. 3)

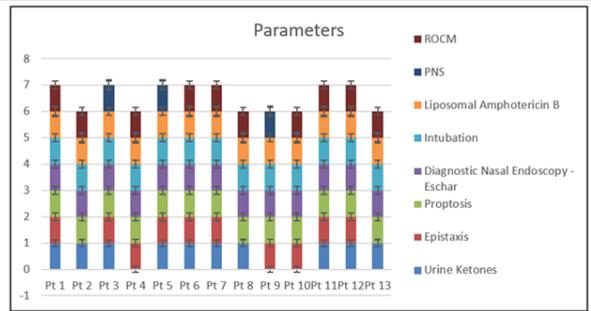


Figure 3. Clinical parameters

Fungal spectrum observed from the study. (Fig. 4)

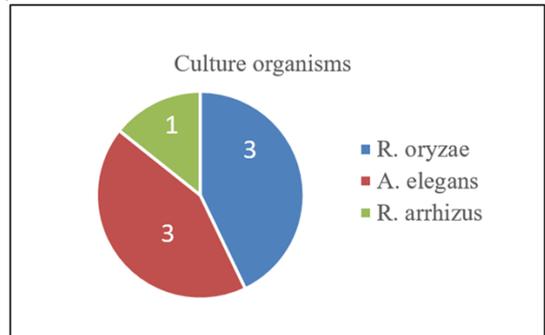


Figure 4. Fungal Spectrum

Age distribution observed from the study – Table 2

Age distribution of cases	
Age (in years)	No. of cases
41 - 45	4
46 - 50	5
51 - 55	4

Health-related Quality-of-life (HrQoL) questionnaire scores and comparison – Table 3.

Paired Samples Statistics							
Comparison units		Mean HUI-3	N	Std. Deviation	Std. Error Mean	HUI-3 Δ	Sig. (2-tailed)
Pair 1	Total Pre-Treatment	0.505	13	0.059	0.016	Reduction	0.059
	Total Post-Treatment	0.358		0.237	0.066		
Pair 2	Survivor Pre-treatment	0.487	5	0.022	0.010	Gain	0.001
	Survivor Post-treatment	0.677		0.054	0.024		

**Discussion**

**Sample size:**

Our study enrolled 16 patients (n=16). 3 patients were discharged against medical advice midway through the treatment citing various issues. Complete clinical data was available only for 13 candidates (n=13). Dropout rate was 18.75%. Studies with a larger sample size with a longer duration have been reported from other centers.<sup>[9]</sup>

**Age and Sex:**

The age range in our study was 41 – 55 years with a mean age of 47.77 ( $\pm$  4.003) years. The peak age of ROCM incidence was 48 years. In other studies<sup>[3,9]</sup>, peak incidence was after the 3rd decade of life with 5% cases reported in children less than 10 years of age and average age at presentation was 48 years.

The male to female ratio in our study was 1:5.5 with a female predominance. This value was not corresponding with other studies which documented a general male predominance.<sup>[5]</sup> The occupation of the majority of individuals was daily wage / coolie workers which comprised 84.62% (n=11) of the study subjects.

**Presenting features:**

The presenting clinical features were broadly categorized into ROCM (n=10, 76.92%) and paranasal sinus (PNS) (n=3, 23.08%) involvement. Epistaxis was by far the most common symptom for ENT referral. The prime factor for paranasal sinus pathology was recent dental extraction (within 3-4 weeks prior to presentation) under poorly controlled diabetic status. Uncontrolled diabetes mellitus type 2 was observed in 92.31% (n=12) and the association was significant (OR-9.2,  $p < 0.001$ ). Recent studies indicate that a fraction of glucose-regulated protein (GRP-78) belonging to the HSP-70 family, is also translocated to the cell surface in many cell types,<sup>[10]</sup> wherein it acts as the receptor mediating penetration and damage of endothelial cells by Mucorales, leading to the observed angio-invasion.<sup>[11]</sup> However, this pathology also occurred in 7.7% of our patients who were otherwise clinically healthy. The clinical course in this subset of patients was less severe. The ROCM type presented with rapid deterioration and multiple cranial nerve involvement and intracranial extension.

The most common cranial nerve palsy noted was Abducent nerve palsy (n=4, 30.77%) and Frontal lobe involvement (n=4, 30.76%) evident with development of lateral rectus palsy and altered sensorium respectively. Magnetic Resonance Imaging (MRI) showed orbital apex and cavernous sinus involvement in 38.46% (n=5). 38.5% had developed ascites possibly indicating gastrointestinal involvement due to dissemination. 7.6% had Hepatitis C Virus (HCV) positivity. Others (92.4%) were seronegative for HIV I/II and HbsAg. No organ transplantees enrolled in our study.

**Diagnostic nasal endoscopy:**

All patients underwent a thorough diagnostic nasal endoscopy (DNE) which revealed eschar involving various segments of lateral nasal wall, nasal septum and nasal floor. Only 1 patient (7.7%) had ROCM with cutaneous involvement (medial canthus). The downside from ENT point-of-view was the delay in referring by primary physicians for endoscopy. The initial treatment regime followed was control of diabetes and resultant control of sinusitis. However, with primary failure of control of either pathologies (diabetes / sinusitis), suggesting a DNE / radio-diagnostics would have added tremendous information on patient status and perhaps changed the course of disease.

**Radiology:**

Computerised tomography scan of brain and paranasal sinuses was done for all candidates. MRI of brain and orbit was done for patients with impending / established intracranial complication to decide on fungal load and feasibility of surgical access and debridement. Characteristic radiological features of fungal involvement were noted.

**Fungal Culture:**

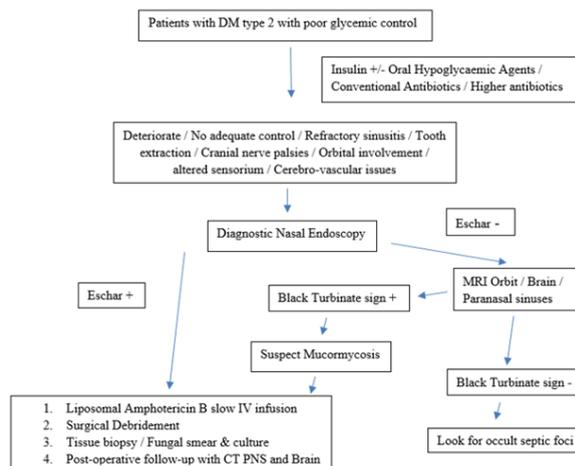
Culture was attempted from the 13 specimens. However, Mucorales were isolated from 7 patients (53.85%) only. The commonest fungi cultured were *Rhizopus oryzae* (n=3), *Apophysomyces elegans* (n=3) – each 42.86% and *Rhizopus arrhizus* (n=1, 14.86%). In other studies<sup>[12,13]</sup>, similar organisms were isolated.

**Management:**

All the patients underwent endoscopic nasal debridement as an emergency procedure with slow IV infusion of liposomal amphotericin B. Total dose given was between 1 – 1.5 gm. Dose monitoring was done with alternate day renal function tests. Post-operatively, all patients were monitored under intensive care setup. Metabolic derangements were promptly corrected. Continuous strict glycaemic control was attempted. 80% of patients of ROCM had overwhelming spread and eventually succumbed to the disease. Survival rate was 38.46%. However, upto 100% mortality was reported in other studies.<sup>[3]</sup>

**Quality-of-Life:**

The mean survivor (n=5) HUI-3 pre-treatment scores were 0.487 ( $\pm 0.022$ ). Mean survivor post-treatment change of score ( $\Delta$ ) by 0.190 ( $\pm 0.032$ ) was statistically significant ( $p = 0.001$ ). However, the QOL assessment done as a single cohort (n=13, total HUI-3) showed no statistically significant change ( $p = 0.059$ ) which could probably be attributed to the high mortality rate observed in mucormycosis.

**Protocol (Fig. 5):**

**Figure 5. Proposed protocol. DM – Diabetes mellitus. CT – Computerised Tomography. MRI – Magnetic Resonance Imaging.**

**Critical appraisal:**

1. Larger cohort study and meticulous treatment protocol with follow-up may enhance outcomes of mucormycosis treatment.
2. Female predominance in this regional population was very evident in our study
3. In sero-negative patients with mucormycosis, DMT2 is the most common risk factor.
4. Tooth extraction in a diabetic individual is a traumatic cause for development of PNS mucormycosis.
5. Evaluation of health-related Quality-of-life.

**Summary / Conclusion:**

- Mucormycosis is definitely a one-way ticket as survival rate is quite low even with advanced medical and surgical options.
- Timely referral by primary care physician to specialty care if disease is refractory to conventional medications / suspect impending complications, would greatly improve treatment quality and thereby provide the individual with a better quality of life.

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