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RHINOCEREBRAL MUCORMYCOSIS: OUR EXPERIENCE

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ABSTRACT

Mucormycosis (phycomycosis, zygomycosis) is a rare opportunistic infection caused by fungi belonging to the Mucorales. It is divided into rhinocerebral, pulmonary, cutaneous, cardiac, gastrointestinal and disseminated, Rhinocerebral form being the most common and most fatal. Mucormycosis is common in immunocompromised individuals and uncontrolled diabetes mellitus is the most common condition. Present study is a prospective study of 10 patients with 6 males and 4 female during period of January 2018 to December 2018. Diabetes mellitus was found in 90% cases and 1 individual was immunocompetent. Histopathology confirmed the diagnosis of mucormycosis. CT scan and MRI were done to assess the extent of disease. Patients were managed with injectable amphotericin B, aggressive surgical debridement and control of underlying condition. Survival rate was 80%. Early diagnosis and treatment is mandatory for a successful management of this infection.

KEYWORDS

Mucormycosis, Amphotericin B, Debridement, Diabetes mellitus.

INTRODUCTION –

Mucormycosis (phycomycosis, zygomycosis) is a rare opportunistic infection caused by fungi belonging to the Mucorales order and the Mucoraceae family. Mucormycosis was first described by Paultauf in 1885 [1]. It represents the third most common angio-invasive fungal infection after candidiasis and aspergillosis [2]. It is more common in immunocompromised patients but can also occur in immunocompetent hosts (such as polytrauma patients). Immunocompromised conditions include; diabetes mellitus (DM), neutropenia, malignancy, chronic renal failure, acquired immunodeficiency syndrome, organ or hematopoietic stem cell transplants. The most commonly reported form of the disease is rhinocerebral mucormycosis which is subdivided into rhinomaxillary and rhino-oculocerebral form. Rhinocerebral mucormycosis is characterized by progressive fungal invasion of the hard palate, paranasal sinuses, orbit, and brain [1]. Inhalation of sporangiospores is the most common route of transmission. Ingestion of spores, direct implantation into injured skin (burns), trauma with contaminated soil, or intravenous (drug users) transmission has also been described. After inoculation it rapidly progresses to vessels, soft tissue, nerves, bone and cartilage producing tissue infarction leading to tissue necrosis and vessel thrombosis. Early diagnosis and aggressive treatment is necessary for this life threating condition.

In present study, we are reporting our experience on 10 cases of mucormycosis presented to ENT department.

MATERIALS AND METHODS –

A Prospective study conducted between the period of January 2018 to December 2018 in ENT department of GMC Nagpur. Study included 10 cases of mucormycosis of nose and paranasal sinuses. Patients with symptoms and signs suggestive of mucormycosis were admitted and were subjected to detailed history and clinical examination, nasal endoscopy, Histopathological examination, KOH and fungal culture examination, radiological examination like CT and MRI. History related to comorbidities like hypertension, Diabetes mellitus, Hansen's disease, Koch's etc. was noted in details. Diagnosed cases of mucormycosis were treated with injection Amphotericin B and endoscopic debridement. Follow up of each case was documented in terms of resolution of disease, complications or death.

RESULTS –

10 patients included in present study with 6 males and 4 females. Age range was between 21 to 70 years with mean age of 42.1 years. Uncontrolled diabetes mellitus was the most common comorbidity seen in 90% cases and 1 patient was immunocompetent. Other comorbidities noted were; Hypertension (60%), Hansen's diseases (10%), Pulmonary Koch's (10%), Pancytopenia (10%), Ischemic Heart disease (10%). One patient was suspected as Alport's syndrome as patient had congenital deafness and Chronic kidney disease.

Patients presented with following symptoms and signs; sinusitis (100%), nasal discharge and blackish crusts in nose (80%), palatal perforation (60%), facial pain and headache (50%), fever, proptosis and diminished vision (40%), septal perforation and bony erosion like middle and inferior turbinate erosions (30%), nasal mass or polyp (20%), necrosis of skin over facial region, intracranial abscess (10%), cavernous sinus thrombosis (20%). All patients reported history of chronic rhinosinusitis. Left sided involvement was noted in 5 (50%) cases, right in 3 (30%) and bilateral in 2 (20%) cases. Isolated maxillary sinus involvement was seen in 5 (50%) cases whereas pansinusitis was seen in 5 (50%) cases. Temporal lobe abscess with fungal granuloma in basioccipital region was detected in 1 case.

Histopathological examination showed numerous broad aseptate fungal hyphae, with a right-angle branching varying from 45 to 90 degree, consistent with the morphology of the order Mucorales (Mucormycosis).

Clinical and radiological profile of patient is tabulated in table no 2.

Treatment consisted of control of underlying disease, nutritional support, systemic antifungal therapy and repeated surgical debridement of necrotic tissues.

MEDICAL MANAGEMENT –

Uncontrolled diabetes mellitus was treated with fractional insulin, basal insulin and oral hypoglycemic drugs. Correction of metabolic acidosis was done if present. Patients with past history of Hansen's disease and Pulmonary Koch's were reassessed for the same though they have completed the previous treatment. Intravenous antibiotics like ceftriaxone, antipyretics and analgesics were given in all patients. Nasal saline drops and saline nasal douching were given to remove nasal discharge and crusts.

Intravenous Amphotericin B was the mainstay of medical treatment at our institute and given in the dose of 40 mg OD for a period of 2-6 weeks depending upon extent and aggressiveness of disease. Renal functions tests were checked on alternate days. Serum creatinine was maintained below 2 mg/ml. In 3 patients, serum creatinine was raised, thus dose of IV amphotericin B was reduced to 20 mg OD. In 2 cases, liposomal Amphotericin B was started as both patients had raised serum creatinine level. Average period of amphotericin injection was 4.12. Low molecular weight Heparin (LMWH) was given in cases of intracranial thrombosis.

SURGICAL DEBRIDEMENT –
Endoscopic surgical debridement was done in all cases to drain purulent nasal discharge, blackish necrotic crust and bony sequestrations. Multiple settings were done ranging from minimum 2 to maximum 7 settings. Average number of settings was 4. Necrosed skin was also debrided wherever involved. Orbital exenteration was done in 1 case. One case with intracranial involvement was referred to neurosurgery for craniotomy and drainage of pus.

OUTCOME –
Outcome of the treatment was measured on the basis of improvement in general condition of patient, reduction in the load of necrotic tissues and discharge on nasal endoscopy. CT scans were done to assess the status of disease. Improvement i.e survival rate was seen in 80% cases with mortality in 20% cases. Follow up nasal endoscopy was done every month and showed no recurrence or residual disease.

DISCUSSION –
Mucormycosis is the third invasive fungal infection after candidiasis and aspergillosis and is caused by fungi of the class Zygomycetes. Rhizopus arrhizus (oryzae) is the most important species. As per the sites of anatomical site involvement, Mucormycosis is divided into 6 types; (i) rhinocerebral, (ii) pulmonary, (iii) cutaneous, (iv) gastrointestinal, (v) disseminated, and (iv) miscellaneous. Chakrabarti et al[3] reported rhino-orbito-cerebral type (44.2%) as most common type of mucormycosis followed by cutaneous (15.5%) and renal (14.0%). Inhalation of sporangiospores is the most common route of transmission. Mononuclear and polynuclear phagocytes of the healthy host are able to kill the spores of Mucorales by generating oxidative metabolites and defensins (cationic peptides). In diabetes mellitus, metabolic acidosis can alter the normal immunologic response of patients to infections. Diabetic ketoacidosis is also known to increase available serum iron, which plays a role in the pathogenesis of the disease [4].The infection may then spread directly to adjacent tissues and structures. Angioinvasion is characteristic of mucormycosis, leading to vascular thrombosis, infarction and subsequent tissue necrosis, with haematogenous dissemination. In present study diabetes mellitus was the most common comorbidity found in 90 % of the patients. One patient had no immunocompromised condition. Many studies have reported mucormycosis in immunocompetent individuals [5,6].

In immunocompetent patients, the nose and/or maxillary sinuses appear to be the predominant source of infection of the respiratory tract. Diagnosis is always misleading and possibly causes delay in treatment. Mucormycosis should be considered among various differential diagnosis like; chronic bacterial sinusitis, sinonasal neoplasms, granulomatous diseases, acute Grave's disease, orbital tumours and pseudo tumours and cavernous sinus thrombosis [7]. In our series, all patients had features of chronic sinusitis.

The incidence of disease has not been demonstrated to vary based on age or gender. In our study we had 6 males and 4 females in age range of 21 to 70 years with mean age of 42.1 years.

Mucormycosis of nose or paranasal sinuses leads to consistent symptoms, sinusitis or periorbital cellulitis, facial numbness, conjunctival congestion, blurry vision, soft tissue swelling, necrosis or eschar formation and necrosis of nasofacial region. Black necrotic intranasal or palatal eschar is highly suggestive of the disease but it occurs in only 40–50 % of those affected [8]. In our study, blackish necrotic crusts were noted in 80% cases and palatal perforation in 40% cases. Advancing infection usually spreads from the ethmoid sinus to the orbit, resulting in loss of extraocular muscle function and proptosis with marked chemosis and can quickly result in cavernous sinus thrombosis, carotid artery, or jugular vein thrombosis (Lemierre syndrome) and death [4]. In present study, we notice internal carotid artery thrombosis in 1 case and cavernous sinus thrombosis in 2 cases. Orbital involvement was noticed in 4 (40%) cases.

Diagnostic armamentarium includes nasal endoscopy, biopsy for Histopathological examination, pus for KOH and Culture and radiological investigations. Early diagnosis is vital in mucormycosis because delay in initiation of treatment can be life threatening due to invasive nature of disease and tendency to embolize to distant organs including brain. CT scan with axial and coronal sections is a highly accurate and noninvasive modality of accurately imaging sinonasal mycosis. MRI of paranasal sinuses and brain helps in assessing intracranial spread and associated thrombosis of major vessels. In present study, CT scan was done in all cases but MRI was done in 5 cases where intracranial complications were suspected.

Spellberg B et al [9] concluded that rapid control of underlying disease process, systemic antifungal and aggressive surgical debridement of necrotic tissue have seen associated with improved outcomes. In our study, treatment modalities were correction of underlying condition, antifungal treatment, surgical debridement. Uncontrolled diabetes mellitus was treated with insulin therapy and correction of metabolic acidosis was done. Nutritional support plays crucial role.

Amphotericin B deoxycholate remains the only licensed antifungal agent for the treatment of mucormycosis. Amphotericin B is a potent nephrotoxic drug and hence requires strict monitoring of renal function tests. Derangement of serum creatinine warrants either reduction of dose or discontinuation of drug. However, lipid formulations of Amphotericin B (liposomal AmB) are significantly less nephrotoxic and can be safely administered at higher doses for a longer period of time than Amphotericin [10]. In a study by Walsh TJ et al, they reported success rate of 1% with amphotericin B lipid complex as salvage therapy for mucormycosis [11]. Treatment with liposomal amphotericin B was associated with a 67% survival rate (16 of 24 patients), compared with 39% survival (24 of 62 patients) with amphotericin B (P = 0.02) among patients with cancer [12]. Thus, liposomal amphotericin B appears to be safer, efficacious alternatives to amphotericin for the treatment of mucormycosis. Dose of Amphotericin B desoxycholate is 1–1.5 mg/kg/d and that of liposomal form is 5 to15 mg/kg/d. It concentrates preferentially in macrophages, infected tissue and shows better CNS penetration [8].

Posaconazole, a new triazole, is an alternative in case of failure, with proven efficacy, good tolerance and fewer side effects; it is administered at 800 mg/d [13].

In present study, amphotericin B was the antifungal agent of choice with alternate day monitoring of serum creatinine. In 3 cases dose was reduced due to raised serum creatinine level and in 2 cases liposomal amphotericin B was given. Average duration of antifungal treatment was 4.12 weeks.

Surgical debridement is combined with medical treatment to achieve rapid control of mucormycosis and is repeated according to evolution. Surgical debridement helps in removal of pus and necrotic debris, hence reduces fungal load and also improves diffusion of antifungal drugs [14]. Debridement should be done till healthy margins. Debridement also includes exenteration of necrotic orbital contents, palatectomy and craniotomy Vironneau, reporting 22 cases of rhino-orbitocerebral mucormycosis, concluded that radical surgery improved local control and survival [14]. Hyperbaric oxygen therapy and cytokines (interferon gamma, GM-CSF) as adjuvants to medical treatment are under assessment. Hyperbaric oxygen therapy has a fungistatic effect and allows revascularization of ischemic tissue [4,13]. In present study we have done aggressive debridement in all cases, with range from 2 to 7 settings. Average number of settings was 4. Craniotomy with drainage of pus was done 1 case where as orbital exenteration was done in 1 case.

In present study, survival rate was 80% with mortality in 20% cases. The overall survival rate of patients with mucormycosis ranges approximately from 50% to 85% with a higher survival rate of rhino-cerebral mucormycosis than pulmonary or disseminated form because the rhinocerebral disease can frequently be diagnosed earlier, and the most common underlying cause, diabetic ketoacidosis, can be readily treated. Disease limited to sinonasal region has mortality be less than 10% [4]. Literature has documented mortality rate of 20-50% [15,16]. Harrill et al in their series reported an overall survival rate of 83% [17].

CONCLUSION –
Mucormycosis of nose and paranasal sinuses is an aggressive and angioinvasive fungal infection, affecting mostly an immunocompromised host. It can present with atypical symptoms and thus can be misled by coexisting infections. High degree of clinical suspicion, presence of predisposing factors, Histopathological examination confirms the diagnosis. CT scan is the main radiological investigation to assess the extent of disease and to monitor the disease progression and recurrence. MRI is useful in intracranial complications. Early diagnosis and appropriate treatment in the form of aggressive surgical debridement, amphotericin B injection and control of underlying condition are keys for better outcome.

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Table no 1 – Clinical profile, radiological findings, treatment and outcome

Case No	Age/ Sex	Clinical features		Comorbidities	Nasal endoscopy	Radiology	Treatment	Outcome
		Symptoms	Sign					
1	23 yr/ M	Lt nasal DS Facial pain Left eye proptosis Fever	Blackish debris and polypoidal mass in Lt nasal cavity, foul smelling purulent Ds, lt eye proptosis Vision – CF5, diplopia, EOM- restricted on lt lateral	DM, HTN	Necrotic crusts, polypoidal mass in MM, septal perforation, purulent Ds in cavity & MS,	CT - Polypoidal mass in lt MM, changes of sinusitis, MO widening, septal cartilage defect, Lt orbital cellulitis. MRI – polypoidal mucosal thickening in LT MS, b/l ES, with fat strands in intra and extraconal space.	Inj Amphotericin B 40 mg OD Fractional Insulin Endoscopic Debridement – 7 setting	Improved after 6 weeks
2	54 yr/ F	Headache Nasal Obstruction Lt Palatal defect Lt facial Palsy Dysphagia High grade Fever	GC Poor Lt LMN grade 5 FN palsy, ulcerative lesion 3x3cm with bony defect over Lt hard palate, LT TM Moderate CP	Uncontrolled DM even after trying multiple regimen, HTN,	Necrotic crust in LT MM, Ethnoidal air cells, necrosis of MT, Septal perforation, purulent Ds in MS.	CT – opacification in Lt MS, ES, MO widening, erosion of posterior wall of LT MS,septal cartilage defect. Lt hard palate defect 3x2.6 cm. LT infraorbital extraconal cellultis	Inj Amphotericin B 40 mg OD reduced to 20 mg OD due to serum creatinine. Fractional Insulin Endoscopic Debridement – 4 settings	Death
3	30yr/ F	b/l Nasal obstruction Ulcer over palate	Blackish Crust in b/l nasal cavity, 3x2 cm mucosal –bony defect in hard palate in midline	DM HTN CKD, congenital deaf	Necrotic crust purulent Ds in Rt Nasal cavity	CT – soft tissue in Rt nasal cavity, mucosal thickening in MS, osteomyelitis of maxilla, and chronic granulomatous infection	Liposomal amphotericin b Fractional insulin Endoscopic debridement – 4 settings	Improved after 4 weeks
4	36yr/ M	Swelling on left side of face Proptosis of left eye Decreased vision Nasal bleeding Fever	Blackish crusts in Lt nose Ulcer & defect Lt hard palate Swelling over Lt forehead Necrosis of Lt orbital content Ulcerative lesion over MC & lower eyelid	DM Uncontrolled	Necrotic crust in Lt nasal cavity, Erosion of septum, lateral wall	CT- soft tissue in Lt MS, erosion of lamina papyracea, necrosis of orbital content, bony defect of 3x4cm over lt hard palate,	Inj Amphotericin B 40 mg OD Fractional and basal Insulin Endoscopic nasal Debridement - 6 orbital exenteration.	Improved in 6 weeks
5	45yr/ M	Lt nasal Ds Facial pain Defect in Lt hard palate	B/L nasal cavity blackish crusts 3x2 cm defect over Lt hard palate	IHD,HTN, DM	Blackish crust in b/l nasal cavity Foul smelling purulent Ds in left MM	Soft tissue changes with air foci in b/l nasal cavity, bony hard palate defect, Lt MS & b/l ES sinusitis.	Inj Amphotericin B 40 mg OD Fractional insulin Endoscopic debridement – 3	Improved in 3 weeks
6	49 yr / M	Facial swelling Rt Nasal obstruction	GC poor Oedema over rt side of dorsum of nose, infraorbital region Crusts in rt nasal cavity	Hansen's disease, DM, Pancytopenia, Sepsis	Blackish crusts in rt nasal cavity, purulent Ds,	Cellulitis over rt side of nose, infraorbital region, opacification in rt MS,	Inj Amphotericin B 40 mg OD Fractional insulin Endoscopic debridement- 2	Death
7	70 yr / M	Diminished vision & proptosis Lt eye Lt hemiparesis Nasal Ds Lt fever	Lt eye CF2, crusts in lt nasal cavity, defect over lt hard palate	DM, HTN, COPD, Pulmonary Kochs	Blackish crusts in Lt nasal cavity, purulent Ds in MM	CT – lytic destruction in Lt MS, bony defect 3x3 cm hard palate, extraconal oedema Fungal granuloma in rt basitemporal region, thrombosis of Cavernous sinus and B/L ICA, rt temporal abscess.	Inj Amphotericin B 40 mg OD Fractional insulin LMW heparin Endoscopic debridement - 4 Neurosurgery opinion – craniotomy with drainage of abscess	Improved in 6 weeks
8	65 yr / M	Facial pain Nasal obstruction Nasal Ds Rt	DNS to rt sharp spur lt, purulent ds	DM, HTN	Purulent ds in b.l MM	Opacification in b.l all sinuses, DNS to Rt with spur on LT	Inj Amphotericin B 40 mg OD Fractional insulin Endoscopic debridement - 3	Improved in 2 weeks

9	28 yr / F	Headache Rt Diminished Vision Rt eye, Nasal obstruction & Ds rt side	Pitting oedema & tenderness over Rt face,Proptosis chemosis Rt eye, CF 2, EOM – restricted in all gazes, Rt hard palate defect, mod CP in Rt TM	DM with ketoacidosis	Blackish crust in Rt Nasal cavity, Purulent Ds in b.l MM, b.l MT & IT necrosis.	CT - Opacification in Rt MS, nasal cavity, SS, ET, SS. Bony defect in hard palate. MRI – Cavernous sinus thrombosis.	Inj Amphotericin B 40 mg OD Basal and Actrapid insulin Endoscopic Debridement - 5 LMW Heparin	Improved in 4 weeks
10	21 yr/ F	Swelling over dorsum of nose, nasal cavity increasing in size	Swelling over roof of Rt nasal cavity just behind vestibule submucousally extending to lateral wall	No	Lt nasal cavity NAD Scope can not be negotiated in Rt nostril. Biopsy taken	Homogenous nonenhancing diffuse lesion present in Rt nasal cavity and Maxillary region, no bony erosion s/o inflammatory changes.	Inj Amphotericin B 40 mg OD Endoscopic debridement – 2	Improved in 2 weeks

M – Male, F- Female, Lt – Left, DM- Diabetes mellitus, HTN – Hypertension, IHD- Ischaemic heart disease, Rt – Right, Ds – Discharge, CF – finger counting, EOM – extraocular movement MM – Middle meatus, MS – Maxillary Sinus, FN – Facial Nerve, TM – tympanic membrane, CP – Central perforation, MT – Middle turbinate, IT – inferior turbinate, SS- sphenoid sinus, FS- Frontal sinus.

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