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Main Article

Rhinocerebral Mucormycosis : A Deadly Disease On The Rise

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Abstract

According to WHO, there will be epidemic of diabetes world over and India is going to be 'A diabetes capital of the world' by 2025. With the increasing incidence of diabetes, the associated complications are also bound to increase. Rhinocerebral mucormycosis is one of them.

Rhinocerebral Mucormycosis is an opportunistic, fulminating fungal infection, caused by Rhizopus species of order of mucorales, frequently seen in diabetic and immunocompromised patients. Mucormycosis has a very high mortality rate.

Early diagnosis and treatment with Amphotericin-B is the key to combat this disease successfully. We have seen 13 cases in last 3 years (2002 -2005) in our area. This incidence is significant, as this type of cases were rarely seen before 2002, in this geographical area. We present an account of these cases; treatment strategies adopted, review of literature, and highlight 'the role of ENT surgeon in diagnosis and management of this dreadful disease'.

Keywords Rhinocerebral Mucormycosis · Mucormycosis · Complications of diabetes · Nasal Endoscopy

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Introduction

Mucormycosis refers to a rare and severe infection with fungi of the order of mucorales. Rhizopus species is the most common organism. Humans usually are resistant to this disease because infection with mucorales spores is a frequent event. Hosts who are immuno-compromised with poorly controlled diabetes mellitus (especially with ketoacidosis), glucocorticoid use, neutropenia in the setting of hematological malignancy, solid malignancy, iron overload, and burns are high risk candidates. The disease is unrelated to age, sex and race because the underlying conditions are the major predisposing factors.

The disease begins in the nose, extends to the facial sinuses and may quickly spread to orbit and brain, producing life threatening orbito cerebral manifestations. The fungus attaches to the nasal mucosa where massive spore formation occurs; then it directly invades the blood vessels, causes arterial thrombosis and ischemic necrosis of the affected part. Extension of disease into maxillary and ethmoid sinuses can lead to orbital involvement. Intracranial spread can occur through ophthalmic artery, superior orbital fissure or cribriform plate.

Material and methods

Charts of 13 patients with histopathologically confirmed diagnosis of ROCM from Jan. 03 to Dec. 05 were analyzed. Evaluation at presentation included a detailed history, ENT, ophthalmic and neurological examination to assess the extent of disease. Initial investigations included complete blood counts, blood urea, s. creatinine, bl. Glucose, blood gas analysis, urine for ketone bodies, and diagnostic nasal endoscopy with biopsy. Diagnosis was made on histopathological examination and KOH preparation. CT scan of PNS and brain were obtained to assess the extent of disease. Treatment with systemic Amphotericin B was started as soon as the diagnosis of mucor was established. Treatment was also instituted to stabilize the underlying metabolic derangement.

After a test dose of 1 mg Amphotericin B in 100 ml of normal saline, 1 to 1.5 mg/kg/day of Amphotericin B was given over 4-6 hours. The dose was increased slowly, monitoring serum creatinine and was continued till a cumulative dose of 3 to 5 gm was reached.

The methodology for staging the disease and the management protocol was adopted from studies by Nityanandam et al in 2003, as we have found it to be the most suitable form of analysis for these types of patients.

We identified 3 distinct clinical stages based on the signs and symptoms and degree of disease progression

Clinical Stages

Clinical stage 1: Signs and symptoms are referable only to Sino-Nasal disease.
Clinical stage 2: Signs and symptoms of Rhino-Orbital disease,
Clinical stage 3: Signs and symptoms of Rhino-Orbito-Cerebral disease,
The study consists of 13 patients with 8 male and 5 female. The age range is 39 to 70 years with an average of 46 years.

Table 1 No. of patients seen and staging applied

No.	Age/ Sex	Status	Area involved with disease	Staging
1.	M/70	DKA	Nose, Palate, Ophthalmoplegia	2
2.	F/46	D K A	Nose, Palate, Ophthalmoplegia	2
3.	F/60	DKA&	Nose, Facial swelling Uremia	2
4	F/42	DKA	Palate, Maxilla, Delirium	3
5.	M/45	DKA	Nose, Ophthalmoplegia	3
6.	M/58	DKA	Nose, Palate, Multiple . cranial nerve palsy	2
7.	M/45	Diabetic	Nose, Maxillary sinus,	2
8	M/51	Diabetic	Nose	1
9	F/39	Diabetic	Headache, Facial edema, Nose.	1
10	M/35	Diabetic	Nasal blocking, Headache	2
11	M/52	DKA	Nose, Maxillary sinus, Orbit	3
12	M/54	Diabetic	Blindness, Nose	2
13	F/51	Diabetic	Headache, Facial edema, Ophthalmoplegia, Palatal infarct, Hemiplegia	3

Treatment Protocol

Three distinct treatment groups were created based on the nature of surgery that the patients underwent.

Group A - Medical treatment with amphotericin B + sinonasal debridement only

Group B - Medical treatment with amphotericin B + sinonasal debridement with orbital exenteration and /or palatal excision.

Group C - Only medical treatment with amphotericin B

Table 2: Showing symptoms and signs of ROCM, according to the stage of presentation

Stages	Nomenclature	Symptoms	signs	No. of pts.
Clinical stage 1	Sino-nasal disease	Headache, Nasal discharge, Facial pain and swelling, Fever	Nasal crusting, Necrosis of turbinates, Palatal necrosis and perforation, Skin erythema of maxillary area	2 Pts
Clinical stage 2	Rhino-orbital disease	Loss of vision, Diplopia	Conjunctival chemosis, Proptosis, Ptosis and ophthalmoplegia	8 Pts
Clinical stage 3	Orbito-cerebral disease	Facial and other palsy, Altered sensorium	Cavernous sinus thrombosis, Altered mental functions, Hemiplegia	3 Pts

Medical treatment

All patients received intravenous amphotericin B as soon as diagnosis of mucor was established. The cumulative dose ranged from 3-5 gm. In patients with rising S. creatinitne, amphotericin B was withheld, till it came to normal and treatment was started again. Stage 1 and 2 patients also received local Amphotericin B with gauze soaked in the solution of 50 mg of amphotericin B (1 amp) in 100 ml of normal saline[2].

No patient could afford lipid soluble (Liposomal) Amphotericin B, so we have not used it.

Surgical treatment

Table 3 Showing clinical stages and treatment strategies

Treatment A	Medical treatment with Amphotericin B + sinonasal debridement only	9 Patients
Treatment B	Medical treatment with Amphotericin B + sinonasal debridement with orbital exenteration and /or Palatal excision.	1 Patient
Treatment C	Only medical treatment with Amphotericin B	3 Patients

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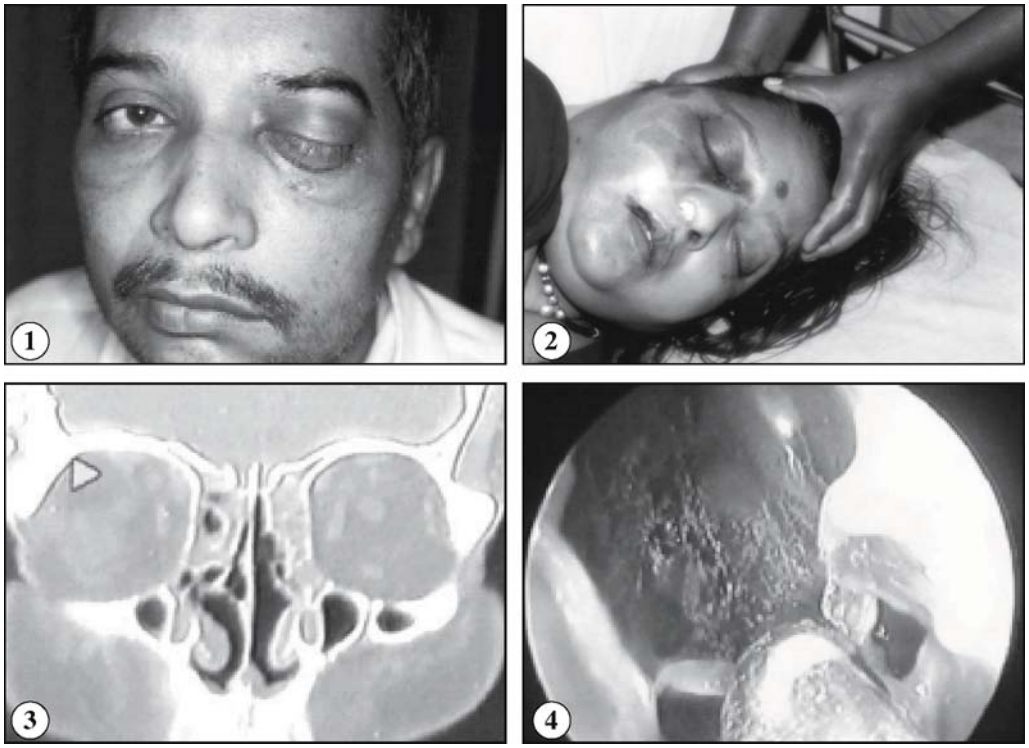

Fig. 1 Photograph of patient showing Proptosis of Lt. eye

Fig. 2 Photograph showing skin erythema of maxillary area

Fig. 3 CT scan "Suggestive of Ethmoidal Sinusitis"

Fig. 4 Endoscopic picture of Blackish, brownish discoloration seen on middle turbinate, septum

One patient underwent orbital extenteration with extensive sinus debridement. None of the patients in clinical stage 3 underwent any surgical procedure. Debridement was done endoscopically(3) Patients in group B and C had more severe metabolic derangement with one patient having more than one underlying disease.

Predisposing conditions

Uncontrolled diabetes was the common underlying disease in all cases, and 7 out of 13 patients had diabetic ketoacidosis. One was in renal failure. No patients from other categories were seen

Outcome

In the clinical stage 1, two patients undergoing Group A treatment had the best outcome with 100% success rate. One patient from stage 2 also received group A treatment because he had total blindness and refused orbital exenteteration. These 3 patients are alive till date. 3 patients with clinical stage 3, died within 2 days of admission, because of uncontrolled disease. Amphotericin B had to be stopped in 2 patients because of deranged kidney function. 7 patients, who were seen in clinical stage 2 and 3 died subsequently because of progression of disease, in spite of treatment. This high mortality rate is consistent with the literature.

Discussion

The World Health Organization predicts that the number of diabetics in India would go up to 40 million by 2010 and 74 million by 2025. Hence, the country stands to become the "Diabetes Capital of the World." having 1/3 of world's diabetic population[4]. With the increasing incidence of diabetes, the associated complications are also bound to increase. Rhinocerebral mucormycosis is one of them. Most reports state that rhino-orbito-cerebral mucormycosis is rather uncommon disease, but the incidence seems to be increasing in our area. Surprisingly in last 3 years we have seen 13 cases. Such cases were not reported earlier from this territory.

The presumed way in which the fungus attacks compromised individuals is fascinating. Iron availability limits the growth of many microorganisms, and this seems to be the case for the phycomycete fungi that cause mucormycosis. Normally, the fungal hyphae produce a substance called rhizoferrin, which binds iron avidly. The iron-rhizoferrin complex is then taken back into the fungus, and the iron becomes available for vital intracellular processes. Human resistance to fungal infection seems to depend to a large degree on non-immune factors.

One of these defense strategies is to limit iron availability to invading microorganisms, by binding the iron to proteins such as apotransferrin[5]. It is clear that a defect in the body's ability to hide iron from invading fungi will predispose to overwhelming fungal attack. Phycomycetes can grow amazingly fast. This has been shown in experiments which looked at Rhizopus as a potential source of protein - it has been estimated that 450kg of fungus, provided with adequate substrate, can produce up to 40kg of (dry weight) protein per hour[6]. It is thus not surprising, that given the right conditions, mucormycosis can within a day, destroy the sinuses and invade the brain of a susceptible person.

Purpose of this article is to draw attention to the clinical presentation and pathogenesis of ROCM and to emphasize the need for high index of suspicion for early diagnosis. Spread of disease is directly proportional to the time delay in the diagnosis except in rare case of indolent variety of disease[7]. In most of the cases delayed diagnosis leads to worsening of disease with fast intracranial involvement. Early diagnosis can pick up the cases in stage 1, when management is much easier and outcome far better.

Initially all our patients were admitted with physicians for control of diabetes and we were called for the consultation for symptoms of nasal obstruction, headache and facial edema. The consultation was sought for after the patient was put on higher antibiotics for couple of days with unsatisfactory response to the treatment. This is probably a common custom in Indian scenario. Most of these were treated on radiological grounds after getting CT scan which was reported as "changes suggestive of ethmoidal sinusitis." It is seen that most clinicians are still unaware of the early clinical presentation of ROCM, because of its' rarity and they treat this "sinusitis" as bacterial. Changes of 'sinusitis' in an uncontrolled diabetic patient should be considered as mucormycosis, unless proved otherwise. Here, the role of ENT surgeon is very important as he is the one, who can suspect and confirm the diagnosis at earliest by nasal endoscopy and biopsy. If we can 'arrest' the disease in nasal cavity itself, the prognosis is definitely going to be better

ENT surgeon is best placed for early diagnosis with endoscopic facility, as disease always begins in nose and spreads rapidly to adjacent vital structures. We strongly recommend diagnostic nasal endoscopy in patients with uncontrolled diabetes with any nasal complaint, facial edema or headache. This is the only way to pick them early. Any blackish discoloration or crusting in the nasal cavity should be sent for KOH staining, fungal culture, and histopathology. In our study 11 cases presented with stage 2 and 3 disease which may be attributed to late presentation or delayed diagnosis, but 2 cases were diagnosed early because of high degree of suspicion by us. The result is that the treatment outcome is better in later cases, which emphasizes the need of early diagnosis. There are reports of managing even stage 3 disease with a lipid-based Amphotericin B preparation given at high daily and cumulative doses[8]. This is not possible in the Indian context for the cost involved in this type of management. None of our patients could afford lipid soluble Amphoterecin B for its cost.

After review of literature we have come to a thought, that if the treatment strategies depending on the clinical stages are adopted, we can certainly offer far better outcome to the patient and can avoid unnecessary disfiguring surgeries like orbital exenteration, maxillectomy, craniotomy etc. in stage 3, where prognosis is known to be fatal.

We would certainly recommend this plan of staging and management, for the study of cases of mucormycosis in future, so that a definite protocol can be standardized.

Conclusion

1 Prognosis of the disease is directly proportional to early diagnosis. The clinicians are still not well versed with the early manifestations to have a high index of suspicion for early diagnosis, which is very crucial.

2 ENT surgeon is best placed for early diagnosis. We strongly recommend diagnostic nasal endoscopy in patients with uncontrolled diabetes with any nasal complaint, facial edema or headache. This is the only way to pick them early.

3 Depending on the renal function, there is no harm in starting Amphotericin B with even with clinical suspicion of the diagnosis of mucormycosis.

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