Main Article

RHINOCEREBRAL MUCORMYCOSIS: AN ANALYSIS OF PROBABLE MODE OF SPREAD AND ITS IMPLICATION IN AN EARLY DIAGNOSIS AND TREATMENT

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ABSTRACT: *The study was done in two parts:*

1. *Analysis of CT scan findings of 17 cases of mucormycosis to determine paranasal sinus, orbital and intra-cranial involvement.*
2. *Cadaveric dissections of the ethmoid complex anatomy to correlate the probable mode of spread.*

Ethmoidal sinus was found to be the most commonly involved. The disease probably appears first here, spreads to orbit through the lamina papyracea and then through the retro-orbital region, intra-cranially. Our aim would be to diagnose the disease at the stage of ethmoid involvement. In immuno-compromised patients, if headache, peri- or retro-orbital pain or blood stained nasal discharge occur, a CT scan of the paranasal sinuses and a nasal endoscopy with biopsy from anterior ethmoids, if this area shows pathology then CT scan must be performed. If this is positive for mucormycosis, surgical debridement of the involved sinuses is to be done and Amphotericin B as intra-venous infusion and treatment of underlying condition is started.

Key Words: *Diagnosis, mucormycosis, therapy*

Rhinocerebral mucormycosis is one of the forms of a fulminant opportunistic fungal infection involving the paranasal sinuses, orbit and brain.

The causative organisms are of the genera Mucor Rhizopus and Absidia, members of the order Mucorales. These are commonly found in soil, vegetable debris and manure. It is characterised by aseptate fungal hyphae.[1] In laboratory, it is grown on Sabraud's medium. The special stain is silver methenamine, where the fungal hyphae are seen black against a green background.

The characteristic feature of the fungus is its remarkable affinity for small and medium sized arteries. It dissects the internal elastic lamina from media, leading to extensive endothelial damage and thrombosis, causing infarction in the tissues supplied. The organism thrives in necrotic tissue and spread by direct extension along injured vessels.[2]

Rhinocerebral mucormycosis is an opportunistic fungal infection, with the commonest predisposing condition being uncontrolled diabetes, especially diabetic ketoacidosis. This is because the organism has an active ketone reductase system, enabling it to thrive in an acid pH 'rich medium'.[3]

Also, acidosis is believed to permit invasion of the blood vessel walls by the fungus.[4] The other predisposing conditions include hepatic coma, urameia, leukemias, aplastic anemias, patients receiving immunosuppresive medications to maintain organ or bone marrow graft viability[5] and it has also recently been reported in HIV-infected patients.[6] However, there have been a few case reports discussing this condition in otherwise normal, i.e. immunocompetent individuals.[7,8]

In an earlier study[9] the orbital and paranasal sinus involvement by mucormycosis had been discussed.

This condition is usually diagnosed late after the occurrence of orbital or neurological signs thereby having a poor prognosis. The delay caused by late occurrence of orbital manifestations has resulted in poor survival rates despite vigorous therapy.[10]

If this condition is diagnosed at the stage of nasal involvement, the prognosis may improve. Hence, if we can postulate the probable mode of spread of this infection, we may be able to diagnose it earlier. This would enable prompt institution of treatment. This may help to avert the grave prognosis of this disease.

MATERIALS AND METHODS

This study was conducted in two parts:

1. A retrospective analysis of CT scan findings of microbiologically confirmed Rhincocerebral mucormycosis. Analysis of CT scans of 17 cases has been

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done (12 males and 5 females). By analyzing these CT Scan findings, a probable mode of spread has been proposed.
2. This was correlated by performing cadaveric dissections of the ethmoid complex anatomy to correlate the probable mode and sequence of disease spread.
3. A case, in which an early diagnosis was made, is discussed.

DISCUSSION

The patients in this series were within the age group of 20-70 years [Table 1]. The CT scan has an important role to play in the diagnosis of Rhinocerebral mucormycosis.[4] On evaluating the CT scans, the commonest sinus involvement was of ethmoid sinus, followed by maxillary sinus. The next commonly involved sinus in this series appeared to be the sphenoid (9/17). However, cavernous sinus thrombosis was rare, being seen in only one case. Frontal sinus was also rarely involved [Table 2]. Intra-cerebral spread was also seen in only four cases but all had a fatal outcome.

Two questions arise, why is the ethmoid sinus commonly involved and what could be its implications in the disease spread and could an understanding of this help in an early diagnosis and management of this condition? Not much emphasis appears to have been given solely to this aspect before (on reviewing literature). As the ethmoid sinus involvement is seen in the majority of cases, it is possible that anterior ethmoids are the first to be involved. Thus, following inhalations of spores in susceptible individuals, germination occurs in the nose and mycelia invade the adjacent tissues (anterior ethmoids). The involvement of anterior ethmoids could be explained by the fact that the main part of the inspiratory air stream passes over the anterior end of middle turbinate (the region of ethmoids). From the anterior ethmoid, the disease spreads to the middle and posterior ethmoids and lamina papyracea. In this study, 13 out of the 14 cases showing ethmoidal involvement showed orbital involvement. Even though the incidence of maxillary sinus involvement was high, of the orbital walls destroyed, the commonest was lamina papyracea. With orbital involvement, only one patient's eye could be saved (rest of the 12 cases with orbital involvement needed an orbital exenteration).

Table 1: Age distribution

Age (years)	No. of cases
20-30	1
31-40	4
41-50	6
51-60	3
61-70	3

Table 2: CT scan findings

Ethmoid sinus	14
Maxillary sinus	13
Sphenoid	9
Frontal	1
Orbit	13
Cavernous sinus thrombosis	1
Intra cerebral spread	4

In the second part of the study, the anatomy of the ethmoid region was reviewed by performing cadaveric dissections. The lateral wall of the ethmoid, i.e. lamina papyracea involvement appears to occur early in the course of the disease, hastening the spread of the disease to the orbit. The anterior and posterior ethmoidal arteries pierce the lamina papyracea and the vessels enter into the roof of nasal cavity[11] (i.e. cribriform plate) interupting the suture line, where the lamina papyracea articulates with the orbital plate of frontal bone. It is possible that lamina papyracea, with its inherant structural weakness, dehiscences, the anterior and posterior ethmoid arteries passing[12] and with possible spread along injured vessels, also contributes to an early involvement of the orbits.

On correlating with the anatomical dissections, the possible portals of intra-cerebral spread could be:
1. Cribriform plate, which is thin and also has preformed pathways in the form of olfactory nerves passing through it.
2. Roof of orbit, which is also very thin.
3. After sphenoid sinus involvement.
4. Through retro-orbital region, which appears to be the commonest in this series. Pilsbury and Fisher[10] also proposed the orbit and important portal of entry of the disease of the CNS.

Thus, the disease appears to occur first in the ethmoid, then through the lamina papyracea it spreads to the orbit and then through retro-orbital region, intra-cranially. Thus, there is possibility of 'Anterior ethmoids as key area' in mucormycosis, where the disease appears first, but remains silent and is only manifest after spread to the orbit. If the disease could be diagnosed at the stage of ethmoidal involvement the patient's eye and may be his life could be saved. A high index of suspicion must be kept in mind in susceptible individuals if retro- or peri-orbital pain, continuous severe usually unilateral, headache and blood stained nasal discharge occur. Smith and Kirchner[13] have also discussed

some probable pathgnomonic signs of developing mucormycosis.

A CT scan of the paranasal sinuses must be undertaken and a nasal endoscopy with biopsy from the ethmoids if disease is seen in this areas mandatory. The specimen should be sent for fungal staining (a 10% KOH mount would give an early result), fungal culture on Sabroud's medium and histopathology. This would enable an early diagnosis before the hall mark sign of 'Black necrosis of the turbinate' is manifest. Pilsbury and Fischer[11] have also noted that fungal infection may have progressed nearly to the orbital apex without development of intra-nasal gangrene. They also perform intranasal biopsies on these patients. The disease is suspected even if necrosis is not present. With the advent of nasal endscopes, endoscopic ethmoid biopsies can be more easily performed. If the specimen is positive for fungus in immunosupressed patients, a three pronged treatment modality in the form of the following is suggested. (1) A radical surgical debridment of the involved paranasal sinuses, (2) Amphotericin B, and (3) most importantly control of the underlying condition is to be undertaken. Bhide et al[9] reported success rate of 73% survival with the above three-dimensional treatment (1) Radical surgical debridment and exenteration of the involved sinuses. As the involved tissue is usually avascular and insensitive dead tissue, the procedure can be carried out under local anesthesia.

Amphotericin B is presently the only available antifungal drug for systemic mycoses. However, it needs to be given as an i.v. infusion, but serious adverse effects are common. A routine hemogram, urine examination, blood urea level, serum creatinine and serum potassuim levels are done as this drug is nephrotoxic if these parameters are within normal limits. The drug is started in the dose of 5 mg given in a 5% Dextrose infusion, monitoring the vital signs. This is because with normal saline, precipitation of Amphotericin occurs. If no side effects occur, the dose is gradually increased up to 1 mg/kg/day. A total dose of up to 1.5-3 g is given. The common adverse effects of this drug include chills, fever, headache, nausea, and vomiting. The most serious side effect is, however, nephrotoxicity and hence weekly monitoring of blood urea and serum creatinine levels is mandatory. If blood urea increases beyond 50 mg per cent and serum creatinine beyond 1.5 mg per cent, the dosage is to be reduced or the drug stopped to be renewed after the repeat parameters are within normal limits. The minor reaction such as fever, chills and rigors can be prevented by a small dose of corticosteroids at the start of the infusion. However, corticosteroids are known to enhance the potassium depleting effect of Amphotericin B and hence should be used in only for a short time and lowest dose that is effective. Also, as the commonest underlying condition is diabetes, blood sugar control may also be affected and hence needs to be monitored. Now, Amphotericin liposomal form is available and is very useful as there is no nephrotoxicity and due to less adverse effects, the patient can be given a dose of up to 2-3 mg/kg daily and so the course is over much faster. It is, however, costly.

The most important factor, however, is treatment of the underlying condition such as diabetic ketoacidosis, renal failure.

CASE REPORT

A 57-year-old diabetic patient on insulin for the last 20 years came with the complaints of severe (L) retro-orbital pain and headache frontal (L) sided for 8 days, the pain and headache were severe, continuous and not relieved by medication of sinusitis. On ENT examination of nose, no obvious abnormality was detected. The CT scan of the Paranasal sinuses showed haziness of the left sided ethmoidal and maxillary sinuses. A nasal endoscopic biopsy of the ethmoids showed a black necrotic mass, which was sent for histopathology, KOH staining and fungal culture. The KOH mount showed no fungus, but as histopathology and fungal culture were positive for mucormycosis. A radical debridement of the involved ethmoid and frontal sinus was done.

The maxillary sinus was tackled by a Caldwell-Luc operation, where the anterior wall of maxilla was found to be eroded and hence after clearing all the necrotic matter the sinus wound was left open, which later healed uneventfully. After 1 week, the patient was started on Amphotercin B intra-venous, which was given as an indoor treatment initially and 15 days later, the patient was discharged form the hospital. The patient continued to receive Amphotericin B (6 h infusion in hospital) on alternate days. Weekly monitoring of hemogram, blood sugar, urea and Serum creatinine was done. Twice the Amphotericin B had to be stopped for 5 days as blood urea had risen, which returned to normal after stopping the drug. A total of 1.5 g was given over a 2.5 months periods

ACKNOWLEDGMENT

We would like to thank the Dr. Suresh Ghaisas, Dean MIMER Medical College Talegaon Dabhade, Pune, for granting permission to perform anatomic dissections at the department of Anatomy of this college.

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