# RHINOCEREBRAL MUCORMYCOSIS : A REPORT OF ELEVEN CASES

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**Abstract.** Rhinocerebral mucormycosis (RCM) is a rare, fulminant fungal infection that usually occurs in diabetic or immunocompromised patients. The mortality rate has been reduced recently with the advent of amphotericin B combined with aggressive surgery. Eleven RCM patients have been treated over the past five years at Srinagarind Hospital. Eight had underlying diabetes, five had renal failure and three of them had both. In eight patients, the diagnosis was established by KOH preparation before histological confirmation. Only two cases revealed positive cultures for *Rhizopus* spp and *Cunninghamella* spp. All patients underwent surgical treatments (extensive debridement, 8 cases; sphenoidectomy, 7 cases; ethmoidectomy 8 cases; maxillectomy 5 cases and orbital exenteration, 6 cases). Amphotericin B was administered to all patients as soon as the diagnosis of RCM was made. Only three patients survived. Early diagnosis and cooperation among ophthalmologist, otolaryngologist and physician are the most important factors for the survival of patients with mucormycosis.

## INTRODUCTION

Mucormycosis is a rare, but frequently fatal fungal infection. The causative organism belongs to four families of the order Mucorales, one of the class Zygomycetes (Phycomycetes). The most important family is the Mucoraceae, which includes the genera *Rhizopus, Mucor* and *Absidia* (Lehrer *et al,* 1980). The terms "phycomycosis" and "zygomycosis" are occasionally preferred, but mucormycosis is the term most frequently used (Parfrey, 1986; Rippon, 1988).

Mucormycosis can present in different clinical forms. The common clinical types include rhinocerebral, pulmonary, disseminated, gastrointestinal and miscellaneous forms (Rangel-Guerra *et al,* 1985). Rhinocerebral mucormycosis is the most characteristic form and frequently involves the structures of the head and neck. It usually occurs in diabetic patients, especially when the diabetes is poorly controlled. The infection usually begins in the paranasal sinus or palate and then invades the adjacent sinuses and retroorbital region. It may also extend through the apex of the orbit into the brain. The fungus has a predilection for growth in blood vessels; thus, cavernous sinus thrombosis and internal carotid artery thrombosis frequently occur (Lowe and Hudson, 1975). The fungus also invades the frontal lobes. This progression of the lesion gives a characteristic picture, with headache, swelling of the face, intranasal necrosis and serosanguinous discharge, marked proptosis, ptosis and ophthalmoplegia and loss of vision are all typically unilateral (Fleckner and Goldstein, 1960; Diamond and Proppe, 1982). Often there are radiologic abnormalities in the paranasal sinuses.

Mucormycosis is appropriately diagnosed histologically when large, broad, nonseptate hyphae with right-angle branching are observed invading tissue. The diagnosis requires a high degree of clinical suspicion, because one of the crucial points in treatment is early diagnosis. Other important factors include systemic antifungal medical therapy, aggressive surgical debridement, treatment of concurrent bacterial infections, and control of the underlying disease (Ferry and Abedi, 1983).

In this paper, we present our experience with rhinocerebral mucormycosis (RCM) patients seen within a five year period at Srinagarind Hospital.

## PATIENTS AND METHODS

All patients were studied at Srinagarind Hospital, Khon Kaen University, Khon Kaen, Thailand, by at least one of the authors between

1986 and 1990, The diagnosis, suspected on clinical grounds, was made by the finding of large, broad, nonseptate hyphae with right-angle branching fungus in KOH wet preparations of aspirated or biopsied specimens. Characteristic fungus on hematoxylin-eosin staining of pathological specimens or isolation of the fungus on culture confirmed the diagnosis.

## RESULTS

Results are summarized in Tables 1 and 2. The Ten patients had pre-existing diseases (eight had a mean age of 45.7 years. Six of them were male. Ten patients had pre-existing diseases (eight had diabetes mellitus, six of whom had not been previously diagnosed. One had diabetic ketoacidosis. Five had renal insufficiency. Thus, three of the ten patients had both diabetes and renal insufficiency). One (case 9) without underlying disease had an unusual presentation which will be described in detail separately. Most common initial complaints were headache, ocular or facial pain followed by loss of vision. The common signs were swelling or tenderness of the face, proptosis, total ophthalmoplegia and blindness, which occurred in our 9 patients; of these, five had bilateral involvement.

In eight of the 11 cases, mucormycosis had been considered as a possibility before histological examination was reported. Of the remaining three cases, the primary physician did not suspect mucormycosis before surgery; therefore, KOH wet preparation and other rapid staining procedures were not performed.

Hyphae were found in pathological specimens of all patients but only two cases (casel and case 10) had positive cultures, which were *Rhizopus* spp. and *Cunninghamella* spp.

All patients received surgical treatment except for case 7, who had a poor general condition and was teminally ill.

Surgical procedures included extensive debridement (8 cases), sphenoidectomy (7 cases), ethmoidectomy (8 cases), maxillectomy (5 cases) and orbital exenteration (6 cases). Timing of surgery ranged from 1 to 15 days after admission (average of fifth day).

Each of the three patients who survived had been treated with surgical debridement, 2000 mg intravenous amphotericin B and oral flucytosine

Table 1

Summary of clinical features of RCM patients.

| Case No. | Age/ Sex | Underlying disease (duration) | Presenting symptoms (duration in days) | Sinuses involvement | Opthalmoplegia/Uni/bilat eye blindness | involvement |
|---|---|---|---|---|---|---|
| 1. | 30 M | RC, RF (10) | Headache (10), decreased vision and Ophthal RE (3) | Pan | +/+ | Bilat |
| 2. | 40 M | RC, RF (4 yr) DM (0) | Right knee bacterial septic arthritis (7), Opthal (2) | Max, Eth | +/+ | Uni |
| 3. | 57 F | DM (0) RF (0) | Fever, Headache (7) Ophthal LE (2) | Pan | +/+ | Uni |
| 4. | 58 M | DM (0) RF (0) | Headache, Ophthal, Blind in RE (3) Ophthal, Blind LE (1) | Pan | +/+ | Bilat |
| 5. | 52 M | DM (0) | Headache (7) Ophthal RE (4) Epitaxis (1) | Pan | +/+ | Bilat |
| 6. | 45F | DM (0) | Ocular pain, Headache Ophthal, Blind RE (5) | Max, Eth, Fro | +/+ | Uni |
| 7. | 52 M | NS, RF (7 yr) | Fever, Ophthal (?) | Pan | +/+ | Bilat |
| 8. | 60 F | DM (1 yr) | Fever (10) Headache, Ophthal, Blind in LE (5) | Eth, Sph | +/+ | Uni |
| 9. | 15 M | - | Nasal congestion (7 month) Headache (30) | Max, Fro | −/− | No |
| 10. | 68 F | DM (5 m) | Headache, Ocular pain LE (3) | Pan | +/− | Uni |
| 11. | 74 F | DM (0) | Headache, Ocular pain (4) Ophthal RE (12) Ophthal LE (7) | Pan | +/+ | Bilat |

Note : Uni = unilateral, Bilat = bilateral, M = male, F = male, RC = renal calculi, RF = renal failure, LE = left eye, RE = right eye, DM = diabetes mellitus, NS = nephrotic syndrome, Ophthal = external ophthalmoplegia, Pan = pansinusitis, Max = maxillar, Eth = ethmoid, Sph = sphenoid, Fro ± frontal, Yr = year, m = month, No = no involvement.

Table 2

Summary of diagnoses, treatments, complications and outcomes of patients with RCM.

| No. | Diagnosis | | | Surgical treatment | Medical treatment | | |
|---|---|---|---|---|---|---|---|
| | Procedure | KOH | Culture | (date of operation) | Ampho B (mg) | 5FC 150 mg/kg | Outcome |
| 1 | Necrotic tissue from maxillary sinus, nasal septum debridement | + | *Rhizopus* spp. | 1) Exenteration R orbit Extensive debridement maxillectomy (2 nd) 2) R Zygoma, arch, hard and soft palate osteotomy, decorticate of temporal bone (20 th) | 2000 | 42 d | Survived : bilateral Blind. |
| 2 | Necrotic material from sinuses, nasal cavity debridement | + | NG | 1) Cald well-Luc, ethmoidectomy (7 th) 2) Orbital exenteration LE | 175 | | Poorly controlled DM Died autopsy : Carebellar hemorrhage Chronic pyelonephritis. |
| 3 | Hard palate ulcer scrape smear | + | NG | 1) Orbital exenteration LE partial maxillectomy Ethmoidectomy Sphenoidectomy (2 nd) | 441 | 10 d | AMI, septicemia Refused further treatment Died |
| 4 | Nasal crust smear | + | NG | 1) Bilateral orbital exenteration External ethmoidectomy, Sphenoidectomy (1 st) | 35 | 2 d | Died due to asphyxia |
| 5 | Nasal crust smear | + | NG | 1) Orbital exenteration RE partial maxillectomy, Ethmoidectomy, Sphenoidectomy nasal septum resection (2 nd) | 526 | 7 d | Died/autopsy: bilateral frontal lobe abscess |
| 6 | Ethmoidal tissue removal | ND | ND | 1) Ethmoidectomy (3 rd) 2) Partial maxillectomy R Orbital exenteration (12 th) | 2020 | 38 d | Survived Blind in RE |
| 7 | Nasal, maxillary necrotic tissue smear. | + | NG | None | 16 | - | Died/autopsy: cerebellar abscess |
| 8 | Sphenoidal tissue removal | ND | ND | 1) External ethmoidectomy Sphenoidectomy (4th) | 1 | - | Refused further treatment Died |
| 9 | Parietal lobe abscess removal | ND | ND | 1) Remove R perietal lobe brain abscess (15 th) | 31 | - | Refused further treatment Died |
| 10 | Middle meatus smear | + | *Cunninghamella* spp. | 1) Ethmoidectomy, sphenoidec tomy, septal resection (7 th ) | 2000 | 10 d | Survived |
| 11 | Sphenoidal necrotic tissue smear | + | NG | 1) Sphenoidectomy (7 th) | 145 | - | Refused further treatment Died |

Note : Ampho = Amphotericin B, 5FC = 5 flucytosine, R = right, L = left, E = eye, NG = no growth, ND = not done, d = day

of 150 mg/kg for 42, 38 and 10 days, respectively.

Of the eight fatal cases, seven died despite early surgical management and administration of amphotericin B. Four died with associated conditions, including poorly controlled diabetes, acute myocardial infarction with gram negative septicemia, asphyxia and end-stage renal failure. These conditions may have been direct or contributing causes of death. Two of the patients who refused further treatment might have survived if they had had ocular exenteration.

## Case report (case 9)

A 15-year old male admitted because of headache for 1 month prior to admission. He was in good health except for a 9 month history of nasal congestion, followed by swelling and induration of his nasal ridge and upper lip for 3 months. He received antituberculous drugs after his nasal skin biopsy showed chronic granulomatous inflammation (acid fast bacilli not found). On physical examination right hemiparesis and papilledema were noted, with an indurated swelling of the nose (Fig 1). He had a normal temperature. The hematocrit was 42 vol % and the white cell count was 8,700/$mm^3$ with 79% neutrophils. The urea nitrogen was 10 mg/dl, creatinine 1.1 mg/dl, glucose 145 mg/dl. The sodium was 132 mEq/l, potassium 5 mEq/l, chloride 104 mEq/l and carbon dioxide 25.8 mEq/l. X-ray showed right pansinusitis. Computed tomographic (CT) scan revealed multiple ring enhancement nodules in the right frontal and right parietal areas (Fig 2) with gyral enhancement

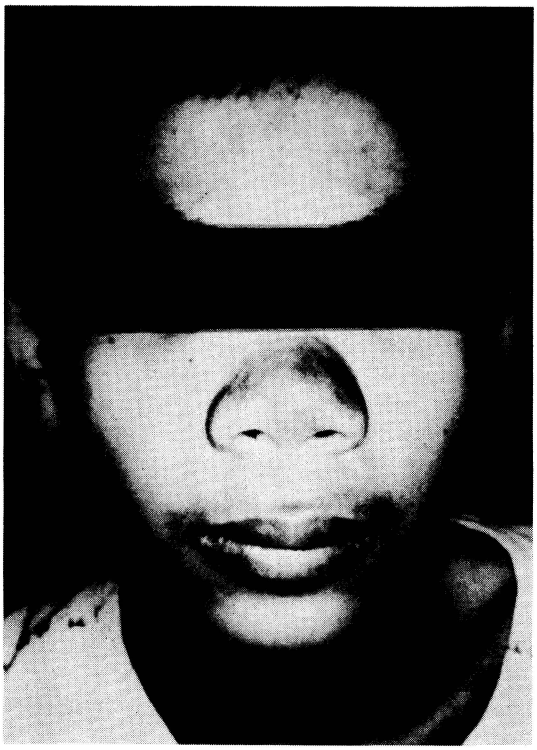

Fig 1—An indurated swelling of the nose in the case report (case 9).

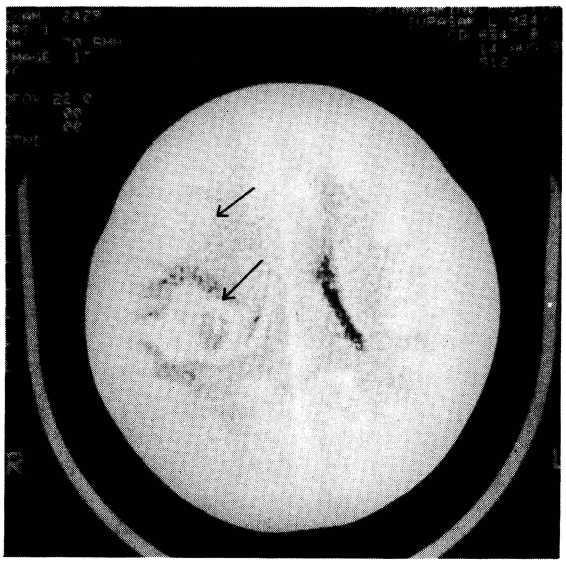

Fig 2—Computed tomography brain scan of the patient showing ring enhancement nodules in right frontal and right parietal areas.

in the left parietal lobe. Multiple tuberculoma was diagnosed and a surgeon was consulted for drainage. Craniotomy and removal of the largest right parietal abscess containing caseous material was done, but the patient had an unsatisfactory recovery. Numerous large, broad, nonseptate hyphae with right angle branching were identified from the pathological specimen. Amphotericin B was promptly administered, but reoperation was not considered due to the patient's poor general condition. He was brought home in a moribund state.

## DISCUSSION

From 1986 to 1990, 11 adult patients with rhinocerebral mucormycosis were seen at Srinagarind Hospital (in the Departments of Ophthalmology, Otolaryngology, Surgery, and Medicine). Even though this is a tertiary referral hospital, 11 cases in 5 years is a large number. This was unlikely to be due to an increased use of immunosuppressive therapy for neoplasia, as other reports have suggested (Lehrer *et al,* 1980; Rangel-Guerra *et al,* 1985; Bendow and Stoddart 1986; Parfrey 1986), as no one had such an underlying malignancy. Rhinocerebral mucormycosis has a strong association with poorly controlled diabetes mellitus (Blitzer *et al,* 1980; Parfrey, 1986), but only one of our diabetic cases had ketoacidosis. However, six of them were unrecognized before admission and metabolic acidosis was established in patients who had both diabetes and renal failure. We found a quite high incidence of renal failure, which is infrequently described. The unrecognized diabetes, the high prevalence of renal stones and renal failure in northeastern Thailand, in addition to the ubiquitousness of the Mucorales are possible explanations for the high number of mucormycosis cases reported here. Early diagnoses in 8 cases were made by KOH preparation of the necrotic material scraped from nasal cavities and sinuses. This simple diagnostic procedure is highly recommended in any diabetic patient who presents with ophthalmoparesis or ophthalmoplegia. It does help in deciding for early aggressive surgical debridement. We also have emphasized the early findings, because this aspect is one of the greatest importance to the clinician confronted with a patient in whom the differential diagnosis rests between mucormycosis in an early stage and some

other type of infectious disease. For example, cases 8, 10 and 11 presented with subacute clinical symptoms without acidosis and without obvious signs and symptoms of nasal cavity and sinus involvement. On the clinical grounds of diabetes presented with ophthamoparesis or ophthalmoplegia and headache, RCM was suspected and diagnosis was confirmed rapidly. The clinician should not be reluctant, therefore, to make a diagnosis and institute immediate treatment for mucormycosis even in the absence of a black eschar (Ferry and Abedi, 1983).

The mortality rate of RCM has recently been reduced with the advent of amphotericin B conbined with aggressive surgical debridement (Blitzer *et al,* 1980; Lehrer *et al,* 1980; Parfery 1986; Ochi *et al,* 1988). But our mortality rate was high (72.7%), even with extensive surgery. This could not be attributed to delayed diagnosis, as only 3 cases were not suspected before the first operation. This was also unlikely to be due to delayed systemic antifungal treatment. It may be partly due to uncontrolled underlying diseases (as in 4 cases), partly to late presentation and partly to the patients and their relatives themselves who refused further extensive surgery. This is an understandable reason because survivors may be left with grave problems requiring extensive plastic repair of residual defects, psychotherapy for emotional difficulties and burdens from blindness. Severity of the rhinocerebral mucormycosis itself is a possible explanation for the high mortality rate, as our cases have a high incidence of total ophthalmoplegia (10 cases), blindness (9 cases) and bilateral involvement (5 cases). Although we had quite early operations, the mean date for surgery being the fifth day, but this may not be early enough for this fulminant devastating disease.

There are also some interesting findings in our cases, as in case 10, in which a Zygomycetes, *Cunninghamella* spp. was found. This organism is a very rare cause of clinical infection (Sands *et al,* 1985). Most reported cases have been in immunocompromised patients and have been associated with vascular invasion, thrombosis, and infarction which are the characteristics of mucormycosis. But it can present as an entomophthoromycosis-like infection (Sands *et al,* 1985). In the described case, RCM occurred in a normal host, which is an uncommon condition (Meyers *et al,* 1979; Pennisi *et al,* 1985) and also presented in an unusual chronic form. The early clinical course which produced localized granulomatous lesions of the mucous membranes of the nose and upper lip is entomophthoromycosis-like; these lesions are benign, usually self-limiting and respond well to local treatment. But in our case the disease progressively invaded the brain and produced multiple brain abscesses, which is a rhinocerebral mucormycosis pattern.

Our experience indicates that RCM is a fulminant fungal infection with a poor prognosis, despite prompt diagnosis, aggressive surgical drainage and amphotericin therapy. However, cooperation among opthalmologist, otolaryngologist and physician is still the most important and relevant factor in survival of this disease.

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