J Microbiol Immunol Infect
2003;36:266-269

Rhinocerebral mucormycosis in Taiwan

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Received: February 13, 2003 Revised: March 4, 2003 Accepted: March 31, 2003

To understand the demographic as well as clinical characteristics, and outcomes of patients with rhinocerebral mucormycosis in Taiwan, we retrospectively analyzed patients with this disease admitted to Chang Gung Memorial Hospital-Kaohsiung from 1988 through 2000. The 21 patients included 8 men (28%) and 13 women (62%). The median age was 60 years (range, 34-82 years). Twenty patients (95%) had underlying diabetes mellitus. The most common clinical feature at admission was ocular lesions, followed by headache, nostril lesions, and consciousness disturbance. Fifteen (94%) of 16 patients who received combined surgical debridement and therapy with amphotericin B survived, while only 1 (20%) of the 5 patients who received amphotericin B alone survived (p=0.004). The diagnosis of rhinocerebral mucormycosis was delayed in 4 patients (19%). Of the 16 patients who survived, 1 (6%) had delayed diagnosis, while of the 5 patients who died, 3 (60%) had delayed diagnoses (p=0.028). This series disclosed a higher proportion of patients with rhinocerebral mucormycosis in Taiwan had underlying diabetes mellitus, and ocular lesions were more frequent than nostril lesions at the time of admission. These results highlight the importance of the timely initiation of a combination of aggressive surgical debridement and treatment with amphotericin B in patients with rhinocerebral mucormycosis. Considering the high rate of delayed diagnosis, improved clinician's awareness of mucormycosis is extremely important and is in urgent need in Taiwan.

Key words: Amphotericin B, diabetes mellitus, debridement, rhinocerebral mucormycosis

Mucormycosis refers to a group of fungal infections caused by members of the order Mucorales, which belongs to the class Zygomycetes. The most frequent causative agents in humans are the family *Mucoraceae*, which includes the genera *Rhizopus*, *Mucor*, *Rhizomucor*, and *Absidia* [1- 4]. Rhinocerebral mucormycosis is an extremely fulminant infection with rapid progression to death if not treated appropriately [1,2]. Infection usually begins in the nose manifesting with dark, blood-tinged discharge, followed by necrosis of the nasal septum and turbinates spreading to the paranasal sinuses. Eventually, the disease accelerates resulting in periorbital cellulitis and invasion of the orbits, eyes, cavernous sinuses, and brain. The main histological finding is invasion along the elastic lamina of blood vessels with subsequent thrombosis, hemorrhage, infarction, and tissue necrosis. Prompt diagnosis and a timely start of effective treatment are the keys to a satisfactory outcome in patients with rhinocerebral mucormycosis. This demands clinician's alertness to the potential for this disease in patients with warning signs and symptoms. However, lack of clinician awareness due to the rarity of the disease entity may result in delayed diagnosis. To understand the demographic as well as clinical characteristics, and outcomes of patients with rhinocerebral mucormycosis in Taiwan, we performed a retrospective study on patients suffering from this disease entity admitted to Chang Gung Memorial Hospital-Kaohsiung (CGMH-KS), a 2500-bed medical center in southern Taiwan.

Materials and Methods

Medical records of patients with diagnosis of rhinocerebral mucormycosis treated at CGMH-KS between March 1988 and May 2000 were reviewed. The diagnosis of mucormycosis was made based on the histopathological finding of characteristic broad nonseptate hyphae with right angle branching in hematoxylin-eosin-stained biopsied soft tissues from the rhinocerebral area, coupled with the presence of compatible clinical features of the illness. Data on demographic characteristics, underlying diseases, clinical presentations, specifically involved sites, laboratory analyses, treatment modalities and clinical

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outcomes were collected. Hyperglycemia was defined as a blood sugar level ≥250 mg/dL [5]; hypoglycemia as a blood sugar level <50 mg/dL; leukocytosis as a peripheral white blood cell (WBC) count >10 000/μL; and leukopenia as a peripheral WBC count <4000/μL. A delayed diagnosis was defined as one made more than 7 days after admission due to rhinocerebral mucormycosis. Demographic, clinical, and laboratory data, as well as treatment-modalities were compared between patients who survived and those who died of rhinocerebral mucormycosis. Mann-Whitney U test was used for comparison of continuous variables, and chi-square or Fisher's exact test for comparison of dichotomous variables. A difference with 2-tailed $p<0.05$ was considered statistically significant.

Results

A total of 21 cases of rhinocerebral mucormycosis were identified. These included 8 men (38%) and 13 women (62%), all of whom were admitted due to rhinocerebral mucormycosis. The median age was 60 years (range, 34-82 years) (Fig. 1). All patients had at least one underlying disease. The most common underlying disease was diabetes mellitus (95%, 20/21), followed by cerebrovascular accident (CVA) (14%, 3/21), and chronic renal failure (10%, 2/21). The demographic characteristics and associated underlying disorders are summarized in Table 1.

At admission, 12 patients (57%) had symptoms and/or signs related to ocular damage, including blurred vision, blindness, ophthalmoplegia, ptosis, proptosis, or orbital swelling, while 9 patients (43%) complained of headache, and 7 (33%) had nostril involvement, including nasal stuffiness, epistaxis, purulent discharge, or rhinorrhea. The clinical manifestations are summarized in Table 2. A total of 17 patients had blood sugar assayed at admission. Of the 11 patients (65%) with hyperglycemia, 3 developed the complication of non-ketotic hyperosmolar hyperglycemic (NKHH) syndrome and 2 developed diabetic ketoacidosis (DKA). One of the patients had hypoglycemia. Of the 19 patients for which hemogram data at admission or pretreatment were available, 12 (63%) had leukocytosis

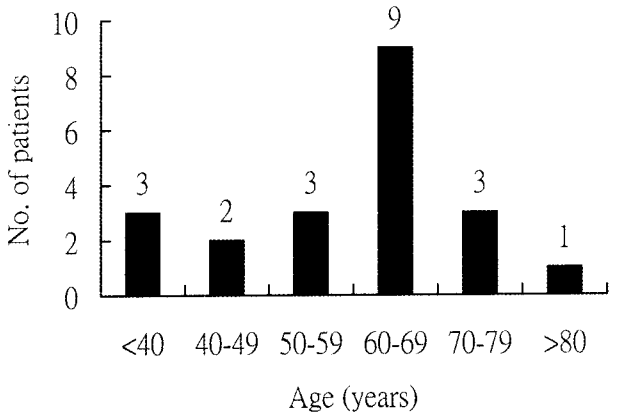

Fig. 1. Age distribution of patients with rhinocerebral mucormycosis.

Table 1. Demographic data and underlying diseases of 21 patients with rhinocerebral mucormycosis

Variable	No. of cases (%)
Sex	
Male	8 (38)
Female	13 (62)
Age (year)	
Mean ± SD	58 ± 13.1
Median (range)	60 (34-82)
Underlying diseases[a]	
Diabetes mellitus	20 (95)
Cerebrovascular accident	3 (14)
Chronic renal failure	2 (10)
Liver cirrhosis	1 (5)

[a]One patient might have more than 1 underlying disease.

Table 2. Clinical features and laboratory findings in patients with rhinocerebral mucormycosis

Variable	No. of cases (%)
Symptoms/signs (n = 21)	
Ocular involvement[a]	12 (57)
Headache	9 (43)
Nostril involvement[b]	7 (33)
Consciousness disturbance	6 (29)
Facial swelling	6 (29)
Fever	5 (24)
Hard palate necrosis	2 (10)
Vomiting	1 (5)
Dizziness	1 (5)
Toothache	1 (5)
Laboratory at admission	
Leukocytosis[c] (n = 19)	12 (63)
Normocytosis[c] (n = 19)	7 (37)
Hyperglycemia[d] (n = 17)	11 (65)
NKHH syndrome (3/17)	3 (18)
DKA (2/17)	2 (12)
Hypoglycemia	1 (6)

Abbreviations: NKHH = nonketotic hyperglycemic hyperosmolar syndrome; DKA = diabetic ketoacidosis

Note: One patient might have more than 1 symptom/sign.

[a]Including blurred vision, blindness, ophthalmoplegia, ptosis, proptosis, and orbital cellulitis.

[b]Including nasal stuffiness, purulent discharge, rhinorrhea, and epistaxis.

[c]A total of 19 patients had hemogram data available at admission or pretreatment.

[d]A total of 17 patients had values of blood sugar available at admission.

with a left shift, and 7 (37%) had normal peripheral WBC.

Of the 20 patients with imaging study results available (19 with computer tomography [CT] scan, and 1 with magnetic resonance imaging [MRI]), 17 were found to have bony destruction and soft tissue swelling with paranasal sinuses and/or intraorbital myositis (2 patients also had cavernous sinus thrombosis), while the remaining 3 had nonspecific soft tissue inflammation.

A total of 16 patients (76%) survived. Among them, 15 received a combination of amphotericin B treatment and surgical debridement under preoperative imaging guidance, and 1 was treated with amphotericin B alone. Nine (56%) of the survivors developed complications, including blindness in 7 (44%), ophthalmoplegia in 2 (13%), cavernous sinus syndrome in 2 (13%), and acute exacerbation of chronic renal failure in 1 (6%) leading to the initiation of maintenance hemodialysis. One female patient (6%) had relapse of mucormycosis 1 month after cessation of treatment with a total of 460 mg amphotericin B, and she was subsequently free from sequelae after completing another course of therapy with 810 mg amphotericin B. The demographic, laboratory, and treatment modality differences between patients who survived and those who died of rhinocerebral mucormycosis are shown in Table 3. Fifteen of 16 patients who received combined surgical debridement and therapy with amphotericin B survived, while only 1 of the 5 patients who received only amphotericin B treatment survived. The survival rate of patients who received combined surgical and medical treatments and of those who received medical treatment alone were significantly different (94% vs 20%; p= 0.004). Of the 5 patients (24%) who died, 3 initially had a misdiagnosis of meningitis; 1 was found to also have aspiration pneumonia with septic shock; and another 1, whose family refused surgical debridement, developed rapidly progressive rhinocerebral mucormycosis. Among the total of 4 patients who had a delayed diagnosis of rhinocerebral mucormycosis, 3 patients (75%) died. The mortality rate was significantly higher in patients with a delayed diagnosis of mucormycosis (60% vs 6%; p=0.028).

Discussion

There was a predominance of female patients (62%) in this study. The ages of patients were widely distributed with a peak prevalence between 60 and 70 years. The most common clinical manifestations were symptoms and/or signs related to ocular damage, followed by headache, nostril involvement, consciousness disturbance, facial swelling, and fever. These findings differ from those observed by Ferguson [6], who found that fever and nostril involvement were the most frequent characteristics. Ninety-five percent of our patients had underlying diabetes mellitus, which was much higher than the 70% rate reported by Blitzer *et al* [7]. In general, patients with diabetes are considered to be immunocompromised. However, the exact mechanism responsible for the increase in vulnerability of diabetic patients to mucormycosis remains unclear [1,6]. Among the 11 patients in our series with hyperglycemia at the time of admission, 3 had the complication of NKHH syndrome and 2 had DKA. Underlying diabetes mellitus predisposes patients to mucormycosis, while its acute complications such as NKHH syndrome or DKA accelerate the growth of Mucorales, which leads to a rapidly progressive clinical deterioration if the patient is not treated effectively [4, 8]. Therefore, reversing the underlying metabolic disorders such as hyperglycemia, NKHH syndrome and DKA is also important in controlling the clinical progression of mucormycosis [1,14].

Hematological neoplasms or immunosuppression resulting from therapy for malignancy are also important predisposing factors to mucormycosis [1,3,

Table 3. Differences in demographic, laboratory, and clinical characteristics, as well as treatment-modality differences between patients who survived and those who died of mucormycosis

Variable	Outcomes		p
	Survived (%) (n = 16)	Fatal (%) (n = 5)	
Sex (M:F)	6:10	2:3	1.000
Median age (year) (range)	60 (34-82)	60 (38-78)	0.649
Delayed diagnosis	1 (6)	3 (60)	0.028
Leukocytosis	8 (50)	5 (100)	0.075
Hyperglycemia	8 (50)	4 (80)	1.000
Therapy with AMB + surgery (n = 16) / therapy with AMB alone (n = 5)	15 (94)/ 1 (6)	1 (20)/ 4 (80)	0.004

Abbreviation: AMB = amphotericin B

9]. In these vulnerable populations, however, pulmonary or disseminated mucormycosis is commonly seen [10, 11]. Rhinocerebral mucormycosis may occasionally develop in otherwise healthy persons [12,13].

Thirty-three percent of patients in this series had a normal peripheral WBC, which indicates that mucormycosis cannot be excluded in clinically suspicious patients, even when their peripheral WBCs are normal. Imaging studies in our series seemed to be helpful not only in clinical diagnosis but also in evaluating the severity of invasive rhinocerebral mucormycosis.

A daily amphotericin B dose of 1 to 1.5 mg/kg/body weight has been suggested for patients with rapidly progressive mucormycosis, while a daily dose of 0.8 to 1 mg/kg/body weight had been suggested for patients with mucormycosis under control. A total of ≥2 g is generally advocated [6,10,14]. The optimal dose of amphotericin B for treatment of rhinocerebral mucormycosis has not yet been determined. In practice, the indicated duration of amphotericin B therapy usually depends on the clinical severity of mucormycosis, treatment response and adverse effects caused by the antifungal agent. Remarkably, 1 patient in status post debridement in this series suffered from a relapse of mucormycosis 1 month after amphotericin B was discontinued by a suboptimal total dose of 460 mg had been used. This patient was subsequently cured after a further dose of 810 mg was prescribed. The relapse in this case suggests that the optimal dose of amphotericin B for treatment of mucormycosis falls somewhere in between 460 and 1270 mg. Further study with a larger sample size is needed before the optimal dose of amphotericin B used for mucormycosis can be established.

In conclusion, ocular or nostril lesions, accompanied with headache, fever or consciousness disturbance, are important clinical signs of rhinocerebral mucormycosis, especially in diabetic patients. This study found that, in comparison to other series, a higher proportion of patients with rhinocerebral mucormycosis in Taiwan have underlying diabetes mellitus, and that ocular lesions are more common than nostril lesions in these patients upon admission. Sinus CT or MRI is helpful in evaluating the severity of mucormycosis, as well as in providing important information regarding landmarks for surgical debridement. A combination of aggressive surgical debridement and treatment with amphotericin B should be started as soon as possible. In view of a substantial delayed diagnosis rate of 19% in this series, widespread clinician awareness of mucormycosis is extremely important, and is in urgent need in Taiwan.

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