The Journal of Laryngology & Otology, 1 of 4.

doi:10.1017/S0022215111001289

MAIN ARTICLE

Endoscopic management of rhinocerebral mucormycosis with topical and intravenous amphotericin B

B SAEDI[1], M SADEGHI[1], P SEILANI[2]

[1]*Otolaryngology Department and* [2]*Medical School Student of Otolaryngology, Tehran University of Medical Sciences, Iran*

Abstract

Objective: Mucormycosis is an aggressive fungal infection which may still cause fatal complications. However, the rarity of this disease has made optimal treatment a controversial issue. This study aimed to evaluate the use of topical amphotericin B in endoscopic management of rhinocerebral mucormycosis.

Subjects and methods: Thirty patients with infection limited to the nose and sinuses were selected. Patients underwent endoscopic debridement of all necrotic tissue; cottonoid pledgets soaked in amphotericin B solution were then placed in the nasal cavity. Subsequently, long-term antifungal therapy was administered.

Results: The overall survival rate was 60 per cent (18 cases); survival rates in the diabetic and malignancy groups were 70.58 and 40 per cent, respectively. Apart from predisposing factors, orbital and maxillary sinus involvement also had a significant correlation with patient outcome.

Conclusion: Topical use of amphotericin B combined with endoscopic surgical debridement, followed by intravenous amphotericin B treatment, may constitute acceptable management for selected patients, with less morbidity than conventional treatments.

Key words: Mucormycosis; Zygomycosis; Endoscopic Surgery; Topical Treatment; Antifungal Therapy; Amphotericin B

Introduction

Mucormycosis is an aggressive fungal infection which may still cause fatal complications in immunocompromised and diabetic patients.[1,2] This fungus is angioinvasive and causes thrombosis of vessels, with consequent black necrosis of nasal and sinus tissue.[3] Despite tremendous progress in the treatment of rhinocerebral mucormycosis, it still has a high mortality rate especially in immunocompromised patients. However, conventional treatment can itself cause substantial morbidity.

Most authors recommend prompt surgical debridement and long-term antifungal therapy. Surgery is used to remove necrotic tissue, reduce the concentration of fungal spores and facilitate the effect of antifungal drugs.[4,5] Reversal of predisposing factors is an indispensable part of treatment.[6–8]

Traditionally, some authors have recommended aggressive surgical resection of affected tissue.[9,10] However, following wide application of nasal endoscopy in sinus surgery, other authors have reported comparable results with frequent endoscopic debridement.[1,11–13] These authors have claimed that, in selected cases, this method has less morbidity, a better surgical field of vision, and comparable results.[2,11,12] However, the poor state of most infected patients results in high mortality rates regardless of treatment type. As a result, much research has been conducted in an attempt to improve treatment outcomes.

Of the different treatment modes available, the addition of topical amphotericin B to conventional therapy is an interesting option. In this study, we evaluated patient outcomes following the use of topical amphotericin B during endoscopic management of rhinocerebral mucormycosis.

Subjects and methods

Study subjects

Thirty-eight consecutive patients referred to the ENT department of a tertiary referral centre (the Imam Khomeini Medical Center) were recruited to the study between May 2006 and April 2010. Of these, eight patients were not eligible for endoscopic resection and were thus excluded from the study. The remaining 30 patients were evaluated. The characteristics of the

Accepted for publication 3 January 2011

excluded patient were used for comparison in some parts of the study.

Inclusion criteria

We included in the study patients suffering from symptoms suggestive of mucormycosis, in whom nasal endoscopy confirmed the presence of necrosis. All patients underwent computed tomography (CT) scanning (and magnetic resonance imaging in some cases) to determine the extent of infection. Additionally, biopsies of involved tissues were evaluated pathologically and biologically to establish a definitive diagnosis, prior to treatment. However, in critical cases we did not wait for the results of analysis before commencing treatment.

Exclusion criteria

We excluded from the study patients with central nervous system (CNS) involvement, extensive orbital involvement or palatal necrosis.

Ethical approval

The study protocol was approved by the institutional review board of the Tehran University of Medical Sciences. Detailed information about the study was provided for participants, and written, informed consent was obtained from each one. All aspects of the study were conducted according to the Declaration of Helsinki.

Procedure and medical treatment

Based on findings from endoscopy and imaging, all patients underwent endoscopic sinus debridement under the supervision of the senior author, using the same technique. During surgery, all necrotic tissue was removed down to the level of viable tissue. In addition, all involved sinuses were opened to facilitate drainage of fungal elements. Any suspicious tissue was examined using frozen section analysis.

After the completion of surgery and achievement of haemostasis, cottonoid pledgets soaked in amphotericin B solution were placed in the nasal cavity for 15 minutes. This process was repeated once daily for five consecutive days.

All patients were also treated with intravenous amphotericin B (1 mg/kg/day), receiving at least 3 g of the drug, in addition to reversal of predisposing factors.

Patient variables and follow-up period

We evaluated patients' demographic data and their results for complete nasal endoscopy and CT scanning. Each patient's clinical presentation and predisposing factors were assessed. Biochemical indices and treatment complications were obtained from patients' medical records.

After surgical debridement, all patients were followed up for at least one year to detect recurrence. Post-operative nasal endoscopy was conducted, under local anaesthesia, in order to remove crusts and to examine the nasal and sinus cavities for recurrence, until healing was complete. Any patients with recurrence underwent repeated endoscopic surgery

Statistical method

Data were analysed using the Statistical Package for the Social Sciences version 11.5 for Windows software program (SPSS Inc, Chicago, Illinois, USA). The chi-square test was used to evaluate pre-operative and post-operative values, and the *t*-test to compare mean values. The Mann–Whitney test was also utilised. Values were evaluated using descriptive statistical methods (mean ± standard deviation (SD)). Results were considered significant if the value of p was less than 0.05.

Results

During the study period, 38 patients were recruited to the study. Of these, eight patients had extensive involvement beyond the sinuses, which necessitated the use of conventional methods besides endoscopic surgery. These eight patients were excluded from the study, but their characteristics are used for comparison in some parts of this report.

Of the original 38 patients, 10 (26.3 per cent) were female and 28 (73.7 per cent) male, with a mean age of 49 ± 19.3 years (range, 16.7–80 years).

The most common predisposing factor in this series was diabetes mellitus. Patients' predisposing factors are summarised in Table I. Only one of the diabetic patients had ketoacidosis at the time of mucormycosis diagnosis.

The mean delay between clinical presentation and diagnosis was 13.5 ± 7.6 days, and the mean delay between clinical presentation and commencement of treatment was 16.6 ± 7.7 days.

Patients' clinical presentations are summarised in Table II.

All patients underwent CT scanning and nasal endoscopy. These results are summarised in Table III. According to imaging and nasal endoscopy, 10 (26.3 per cent) patients had bilateral involvement, 15 (39.5 per cent) had unilateral left involvement and 13 (34.2 per cent) had unilateral right involvement.

TABLE I
PATIENTS' PREDISPOSING FACTORS

Factor	*n* (%)
Diabetes	22 (57.9)
Malignancy	12 (31.6)
Organ transplantation	1 (2.6)
Other	3 (7.9)

TABLE II
PATIENTS' CLINICAL PRESENTATION

Symptom	*n*	%
Nasal obstruction	13	34.2
Nasal discharge	5	13.3
Headache	20	52.6
Cheek anaesthesia	17	44.7
Periorbital oedema	18	47.4

TABLE III
RESULTS OF IMAGING AND DIAGNOSTIC NASAL ENDOSCOPY

Parameter	Value
Lund–Mackay score (mean ± SD)	5.85 ± 3.7
Septal involvement (pts (*n* (%))	17 (36.9)
Middle turbinate involvement (pts (*n* (%))	17 (36.9)
Involvement beyond septum & turbinate (pts (*n* (%))	12 (26.2)

SD = standard deviation; pts = patients

Medical treatment was commenced before surgery in 30 (78.9 per cent) patients, and after surgery in the remainder. Recurrence was detected in 10 (21.4 per cent) patients, once in six (15.8 per cent) patients and twice in four (10.5 per cent) patients. The mean duration of treatment was 32 ± 13 days.

The overall patient survival rate was 60 per cent (18 patients). Twelve (40 per cent) patients died. By comparison, the patients who were excluded from the main series and received conventional treatment had a survival rate of only 37.5 per cent (three patients) ($p = 0.303$; chi-square test). The causes of death in the endoscopic patients are presented in Table IV.

In this series, there was no significant relationship between survival and age (using the *t*-test), sex or different symptoms (using the chi-square test). Moreover, we found no significant correlation between Lund-Mackay score and survival (using the Mann–Whitney test). The time delay between diagnosis and treatment did not correlate with survival. Of the different sites of involvement, only maxillary sinus involvement showed a significant relationship with poor prognosis ($p = 0.015$; chi-square test). During treatment, five patients required orbital exenteration, all of whom died; therefore, this procedure can be considered a prognostic factor ($p = 0.01$; chi-square test). The delay between diagnosis and treatment did show any significant relationship with prognosis. The extent of necrosis seen on pre-operative diagnostic nasal endoscopy did not correlate with survival. However, there was a significant difference between the survival rates of diabetic patients (70.58 per cent) and patients with malignant disease (40 per cent) ($p = 0.019$; chi-square test). Laboratory results and biochemical indices were also analysed, as shown in Table V.

TABLE V
BLOOD CELL COUNTS AND BIOCHEMISTRY INDICES, BY SURVIVAL

Parameter	Patients		*p*
	Survived	Deceased	
WBC (ell/ml)	10 500 ± 4650	29 900 ± 65 400	0.315
Hg (g/dl)	11.5 ± 1.8	11 ± 2.4	0.536
Platelets (ell/ml)	249 000 ± 110 000	190 000 ± 181 000	0.431
FBG (mg/dl)	176 ± 69	164 ± 85	0.353
BG (mg/dl)	180 ± 62	316 ± 113	0.012*
Na (mg/dl)	139.1 ± 3.9	135.9 ± 4.2	0.062
K (mg/dl)	3.9 ± 0.6	4.1 ± 1.2	0.613

Data represent means ± standard deviations unless otherwise indicated. *Significant (*t*-test). WBC = white blood cell count; Hg = haemoglobin; FBG = fasting blood glucose; BG = blood glucose

Discussion

Despite recent tremendous advancements in sinus surgery, invasive fungal sinusitis still has a high mortality rate. Traditionally, many researchers have recommended aggressive surgical debridement and long-term antifungal treatment.[5,10,12] However, more recently it has become clear that aggressive surgery may cause severe morbidity in survivors. Therefore, many researchers have sought to improve treatment techniques in order to gain better clinical outcomes.

TABLE IV
PATIENTS' CAUSES OF DEATH

Cause	*n*	%
Cardiopulmonary complications	7	58.3
CNS complications	3	25
Sepsis	2	16.7

Of various recent treatment proposals, the direct introduction of amphotericin B to the sinus cavity in order to reduce the density of fungal spores is an attractive option. Because of the adverse renal and hepatic effects of amphotericin B (which can cause serious complications), some researchers have used it topically during treatment.[12,14] However, well designed, controlled studies are needed to evaluate patients' responses to this type of management.

Our patients' overall survival rate was approximately 60 per cent, which was acceptable considering the large number of non-diabetic patients in our series.[4,7,8,15] Moreover, in comparison with the results of conventional mucormycosis treatment at our centre, this survival rate represented a positive improvement.[16] Considering the lower incidence of post-operative complications following endoscopic treatment, and the comparable findings reported by the present study and similar reports, we would recommend our treatment modality in selected cases.[2,11,17]

To the best of our knowledge, and after reviewing data from the Medline and Institude for Scientific Information (ISI) databases, our study is the largest series of endoscopic management of mucormycosis patients published to date. Due to the rarity of this disease, most published studies have not reported large series. Therefore, the results of all such studies, including our own, will be affected by their small sample sizes.[3,8]

Despite these shortcomings, some of our evaluated variables were significantly correlated with patient prognosis.

Maxillary sinus involvement was associated with a significantly poor prognosis.

Orbital exenteration was another significant prognostic factor. All patients with orbital exenteration died of their disease, despite orbital exenteration and aggressive treatment. It seems that, regardless of the type of treatment, rhinocerebral mucormycosis with orbital involvement is resistant to treatment. However, some reports have claimed successful treatment of rhino-orbital mucormycosis.[7,8,13,18,19]

Reviewing our patients' causes of death revealed complications associated with extensive mucormycosis involvement and severe comorbidity. Of the former, CNS involvement can be considered a fatal complication.[3,7,8] However, one of our patients with CNS involvement during the course of treatment went on to long-term survival, despite slight hemiparesis, after two endoscopic treatment procedures.

Mucormycosis is a serious infection and requires prompt surgical treatment in order to improve patient outcomes. Some reports have considered a treatment delay of more than 6 days to represent an indicator of poor prognosis.[8] However, a mean delay of 16.6 ± 7.7 days had no significant relationship with survival in our series. It would appear that reversal of predisposing factors and commencement of antifungal therapy are more effective than early surgery in improving patient prognosis.[12]

Ultimately, the most important prognostic factors in our study, as in other series, were patients' predisposing conditions. Our diabetic patients had a significantly better prognosis than our patients with malignancy. Blood glucose level can be considered an important factor in defining treatment outcome. Although many researchers consider ketoacidosis to be a risk factor for poor prognosis, the small number of patients with this complication in our series caused no significant difference.[10]

- **Mucormycosis is a rare but potentially fatal disease**
- **Defining the best treatment method is difficult, due to the condition's rarity**
- **This study assessed topical amphotericin B plus endoscopic surgical debridement, followed by intranvenous amphotericin B, in 30 patients**
- **Survival rates were 60 per cent (18/30) overall, and 71 per cent in diabetic cases and 40 per cent in malignancy cases**
- **All five patients with orbital involvement died of their disease (despite exenteration and aggressive treatment); maxillary sinus involvement was also associated with a poor prognosis**

Based on the above findings, the treatment modalities used in our series can be considered an effective method, with acceptable complications. This conclusion is in agreement with other studies.[12]

Conclusion

Mucormycosis is a rare condition which can still be fatal. Its rarity has made optimal treatment a controversial issue. A combination of endoscopic surgical debridement plus topical amphotericin B usage, followed by intravenous amphotericin B therapy, is acceptable in the management of selected patients, and has less morbidity compared with conventional treatment.

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Address for correspondence:
Dr B Saedi,
Otolaryngology Research Center,
Imam Khomeini Medical Center,
Tehran University of medical sciences,
Bagherkhan Street,
Chamran Highway,
Tehran 141973141, Iran

Fax: 982166581628
E-mail: saedi@tums.ac.ir

Dr B Saedi takes responsibility for the integrity of the content of the paper
Competing interests: None declared