

## Mucormycosis: a 10-year experience at a tertiary care center in Turkey

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**Background/aim:** Mucormycosis is a rare invasive fungal infection most commonly encountered in the immunocompromised host. We analyzed 51 adult patients treated for mucormycosis between 2003 and 2013 and recorded at a tertiary university hospital in Turkey.

**Materials and methods:** We examined the following data for all patients: age, sex, predisposing disease, symptoms, treatment, surgical procedure, concomitant infections, intensive care requirement, and outcomes.

**Results:** During the study period 51 cases of mucormycosis were documented; 54.9% of the patients were female. The mean age was  $44.2 \pm 18.2$  years. Rhinocerebral presentation was reported in 94.1% of patients. Almost all patients (88.2%) had at least one risk factor. The common predisposing factors were hematologic malignancies (52.9%), diabetes mellitus (25.5%), and solid malignancies (5.8%). The most common initial symptoms were fever, cellulitis, and facial pain. The primary medication used was liposomal amphotericin B or conventional amphotericin B. Surgery was performed in 94.1% of patients. Mortality was 52.9%.

**Conclusion:** Our study revealed that mucormycosis continues to be a mortal disease in about half of the cases. Our findings indicate that treatment with L-AMB is associated with a favorable response. Also, in the case of facial pain, the low mortality rate may indicate the importance of early diagnosis.

**Key words:** Facial pain, fever, liposomal amphotericin, mucormycosis

### 1. Introduction

Mucormycosis is a rare invasive fungal infection most commonly encountered in immunocompromised hosts. Risk factors for the development of mucormycosis include poorly controlled diabetes or diabetic ketoacidosis, prolonged neutropenia, renal disease, liver cirrhosis, high dose steroids, and malignancies such as leukemia and lymphoma. Mucormycosis may also affect immunocompetent patients with trauma and burns, or patients under deferoxamine treatment (1,2).

Aggressive surgery, combined with systemic antifungal treatment, is the main applied treatment modality (3,4). Despite these treatments, mortality and morbidity rates are high. Early diagnosis, underlying disease, and form of mucormycosis are determinative factors for prognosis (2,5).

In recent years, mucormycosis appears to be increasing worldwide (6,7). Thus, we aimed to analyze the local epidemiology and outcome of mucormycosis in our center.

### 2. Materials and methods

The Çukurova University Hospital is a tertiary teaching center with 1200 beds. From January 2003 to May 2013 a total of 51 cases of mucormycosis were recorded at the Çukurova University Hospital. The diagnosis of mucormycosis was confirmed histologically. Patients with a histopathology report of aseptate or pauciseptate, broad, thin-walled fungal hyphae branching at right angles were reviewed.

The demographic characteristics, underlying conditions, site of infection, clinical signs and symptoms of infection, radiological findings, treatments, and outcome were extracted from the clinical records of patients.

#### 2.1. Statistical analyses

Comparisons were made by Fisher's exact and chi-square tests as appropriate. Kaplan-Meier curves were analyzed by the log-rank test. Results were represented as means  $\pm$  SD, median (min-max), and n (%).  $P < 0.05$  was considered as significant. Statistical analysis was performed using SPSS v 20.0.

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### 3. Results

Over the 10-year period, 51 adult patients with mucormycosis were identified. Twenty-eight (54.9%) of them were female. The mean age was  $44.2 \pm 18.2$  (17–85) years. Almost all patients (88.2%) had at least one underlying condition at the time of infection. Underlying conditions are shown in Table 1. Six patients (11.8%) had no predisposing factors.

Sinus involvement consisting of rhinocerebral, sinus, and sino-orbital infections constituted the majority of infections (94.1%). Orbital and cerebral involvement was reported in 27.5% and 19.6%, respectively. Bone destruction was detected in 17 (33.3%) patients, and 5 (9.8%) patients had abscesses. Pulmonary, thyroid, and colon involvement was 2% each.

Twenty-four patients with hematological malignancies (24/27) had the rhino-orbital form and the other three patients had pulmonary, thyroid, or colon involvement. Fourteen (27.5%) of these patients had neutropenia.

In all cases the diagnosis of mucormycosis was made by histopathology.

The most common initial symptoms were fever (70.6%), facial edema (62.7%), and facial pain (49%). Unconsciousness (5.9%), ketoacidosis (5.9%), and rhinorrhea (9.8%) were the other findings. Eight patients (15.7%) had hard palate ulcerations on the nasal mucosa in endoscopic examination.

All patients received medical treatment. The primary medication used was liposomal amphotericin B (L-AMB) (72.5%) or conventional amphotericin B (C-AMB) (27.5%). Maintenance treatment with posaconazole was

used in 11.8% of patients. Hypokalemia (64.7%) and nephrotoxicity (45.1%) were common side effects.

Overall 94.1% of patients had surgery. Thirty-nine (81.3%) of these patients had endoscopic sinus surgery, 7 (14.6%) had open surgery, and two patients had both endoscopic sinus surgery and open surgery. Patients had to be operated on several times due to recurrences. The number of operations was between 1 and 6 (mean:  $1.6 \pm 1.1$ ).

Twenty-seven patients (52.9%) were hospitalized in the intensive care unit and 28 (54.9%) patients had concomitant infection. These infections are listed in Table 2.

Mortality was 52.9%. Sex, cerebral/orbital involvement, presence of risk factors, diabetes, drug side effect, and type of surgery were not associated with mortality. However, concomitant infection, the absence of facial pain and fever at the time of presentation, and treatment with C-AMB were associated with increased mortality. The mortality of patients followed in the intensive care unit was statistically higher than that of the other patients ( $P < 0.005$ ). In patients with facial pain the mortality rate was significantly lower than that in patients without facial pain ( $P < 0.005$ ). The response rate of patients treated with C-AMB was 21.4%, while the response rate was 56.8% in patients who received L-AMB. In our patients, therapy with L-AMB was associated with a favorable response and high survival rates when compared with C-AMB ( $P < 0.05$ ) (Figure).

### 4. Discussion

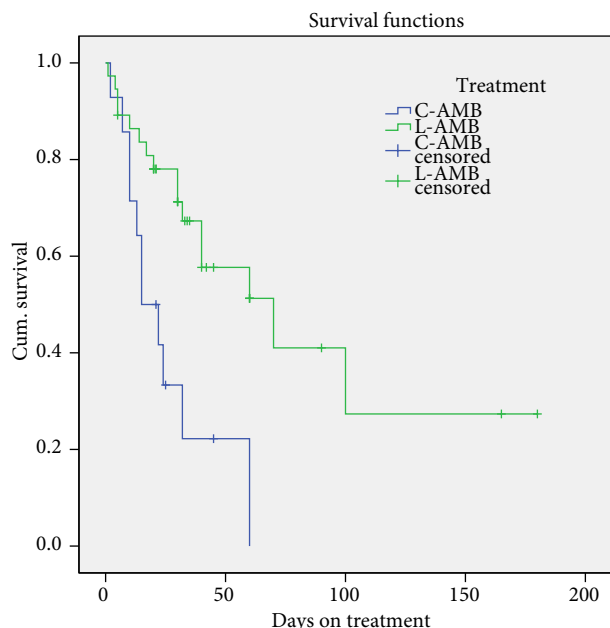
We analyzed 51 adult cases with mucormycosis over a 10-year period. There have been several reports from Turkey, but to our knowledge our report is the largest case series reported from a single hospital (8–10). In a recent report, 151 zygomycosis cases from different centers were evaluated by the pooled analysis method and 87.8% of the cases were diagnosed as the rhino-orbito-cerebral form (11). In most series rhinocerebral infection is the most common clinical presentation (5,7,12). Similarly to these

**Table 1.** Underlying condition of patients.

Underlying condition	Number of patients (%)
Hematological malignancy	27 (52.9)
Neutropenia	14/27 (51.8)
Intensive care unit	16/27 (59.2)
Diabetes mellitus	2/27 (7.4)
Diabetes mellitus	13 (25.5)
Intensive care unit	7/13 (53.8)
Solid malignancy	3 (5.8)
Intensive care unit	3/3 (100)
Renal transplantation	1 (1.9)
Steroid use	1 (100)
Pregnancy	1 (1.9)
Intensive care unit	1/1 (100)

**Table 2.** Concomitant infections.

	Number of patients (%)
Pneumonia	20 (39.2)
Bacteremia	4 (7.8)
Urinary infection + pneumonia	1 (1.9)
Soft tissue infection	2 (3.9)
Pancreatitis	1 (1.9)
Total	28 (54.9)



**Figure.** A comparison of survival times of patients treated with C-AMB and those treated with L-AMB.

reports, almost all of our patients had the rhino-orbito-cerebral form. Pulmonary zygomycosis is more common in patients with hematological malignancies and bone marrow transplantations than other populations (5,7,12). In our hospital, bone marrow transplantation had not been performed in those years; therefore, the distribution of infection may be different from the literature.

In most studies, hematologic malignancy was reported as the most common underlying disease. Ambrosioni et al. reported that hematological malignancy was the most common predisposing factor in a tertiary care hospital and 75% of these patients had allogeneic bone marrow transplantation (7). In the study of Bitar et al. an increased incidence in patients with hematological malignancies was reported; however, Roden et al. reported that the most common underlying condition was diabetes (2,6). In our study the most prominent underlying diseases were hematological malignancies and diabetes mellitus. Solid malignancies, steroid usage, and pregnancy were other predisposing factors. Six patients had no identified predisposing factor. There have been several reports of mucormycosis cases with no predisposing factors (1,13,14).

The diagnosis of mucormycosis is challenging. Antigen detection tests are not available. Therefore, tissue biopsy for histopathology and culture is mandatory for diagnosis. The culture also allows identification on the species level and eventually antifungal susceptibility testing (15,16). In a review of 929 zygomycosis cases, a positive culture

result was obtained in 50% of the cases (2). In our center culture was not feasible due to a number of reasons, such as inappropriate sampling and storage of samples until examined. Therefore, the diagnosis of our patients was confirmed by histopathological and radiological examination in addition to clinical findings.

Mucormycosis was reported primarily in males (65%) by Roden et al. (2). In a case series report from Turkey, 52% of 151 patients were male and the mean age was  $45.4 \pm 21.4$  years (11). The mean age and sex distributions of our patients were similar.

The management of mucormycosis should include antifungal therapy, surgical debridement, and control of underlying conditions. Amphotericin B has shown excellent activity and L-AMB is more effective than the C-AMB in murine models (17). The use of antifungal therapy other than liposomal AmB was reported with increased mortality in many studies. In the study of Roden et al., the response rate of patients who had been treated with C-AMB was 61%, while the response rate of patients who had received L-AMB was 69% (2). In our patients, therapy with L-AMB was associated with a favorable response. Salvage treatment may be necessary and posaconazole is strongly recommended (16). In a review that consisted of 96 mucormycosis cases treated with posaconazole, a complete response was reported in 64.6% of the cases, and overall mortality was 24% (18). Our 6 patients received posaconazole as a maintenance therapy following L-AMB, and only one of these patients died.

Optimal duration of treatment has not been studied previously (16). The mean treatment duration was  $35.6 \pm 35$  days in our patients. ESCMID and ECMM Joints recommend continuing antifungal treatment until a complete resolution as demonstrated on imaging (16).

Clinical trials documented higher survival rates with a combined modality approach of surgical and medical treatment (3,4,16). In a retrospective study, surgical debridement of lung involvement was associated with a decreased mortality from 62% to 11% (19). Most of our patients had surgery. Vironneau et al. showed that surgery is of major importance especially in rhino-orbito-cerebral locations (20). Most of our patients had the rhino-orbito-cerebral form.

Mortality rates varied in the different studies and also according to different underlying conditions and localization (1,2,7,21). Petrikos et al. reported 54% mortality and Lanternier et al. found 44% at day 90 and this differed significantly according to localization (22,23,24). The overall mortality rate of our patients was 52.9%, which is similar to other reports. The mortality of patients followed in the intensive care unit was statistically

higher than that of the other patients. Intensive care patients were followed with the expectation of worsening cases. In our patients, therapy with L-AMB was associated with a favorable response and improved survival rates when compared with therapy with C-AMB. Our findings were supported by Roden et al. and Rüping et al. (2,25). In the patients with facial pain the lower mortality rate may be due to early diagnosis.

In conclusion, our study revealed that mucormycosis continues to be a mortal disease in about half of the cases. Our findings indicate that treatment with L-AMB is associated with a favorable response. Also, in the case of facial pain the low mortality rate may indicate the importance of early diagnosis. Despite the high mortality rates, early and rapid medical treatment combined with surgery seems to be promising for mucormycosis patients.

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