Mucormycosis in paediatric patients: demographics, risk factors and outcome of 12 contemporary cases

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Summary

Mucormycosis is associated with high morbidity and mortality and is perceived as an emerging fungal infection. However, contemporary paediatric data are limited. We present a series of paediatric cases of mucormycosis reported from Germany and Austria collected within a voluntary epidemiological survey through standardised, anonymized case report forms. Twelve cases were reported between January 2004 and December 2008 (six men; mean age: 12.6 years, range: 0.1–17 years). Mucormycosis was proven in nine, and probable in three cases. Isolates included Lichtheimia (syn. Absidia pro parte, Mycocladus) (five), Rhizopus (three) and Mucor (one) species. Infection was limited to soft tissue in three cases, the lung in two cases, and an infected thrombus in one case; rhinocerebral disease was found in three cases, and pulmonary-mediastinal, pulmonary-cerebral and soft tissue-cerebral involvement in one case each. All three patients with isolated soft tissue infection were cured, whereas seven of the remaining patients died (one patient without follow-up). The overall mortality rate was 67%. While these data cannot provide conclusive data on incidence and disease burden of mucormycosis in paediatric patients, they reflect the continuing threat of these infections to immunocompromised patients and the need for improved diagnosis and management.

Key words: Mycoses, mucormycosis, children, neonates, epidemiology, outcome.

Introduction

Zygomycoses are among the less prevalent invasive fungal infections but have exceedingly high fatality rates.1 They are increasingly being recognised in immunocompromised patients, in particular during the recent 5–10 years. This trend is coincident with an increased awareness of mucormycosis and the wider use of voriconazole and members of the echinocandins for prophylaxis and empirical therapy in this population. The rhinocerebral, pulmonary, and disseminated forms are usually seen in patients with underlying haematological malignancies, such as leukaemia or lymphoma, in patients receiving immunosuppressive therapy or corticosteroids and in patients with diabetes. Skin and soft tissue infections are often the result of trauma or burns. Even with early diagnosis and appropriate surgical and medical therapy, the mortality rate is high.1–6 For this reason, a high degree of suspicion is needed, to initiate treatment promptly.

Although mucormycosis is associated with high morbidity and mortality and is perceived as an emerging
fungal infection, contemporary data on demographics, risk factors, management and outcome particularly in paediatric patients are limited.4,5,7–9 In 2004, the European Confederation for Medical Mycology (ECMM) has initiated a prospective survey to collect data on mucormycosis in Europe as a first step to planning strategies for improved diagnostic and therapeutic interventions and outcome of these infections. Herein we present a series of paediatric cases reported to the registry from Germany and Austria from January 2004 until December 2008.

**Patients and methods**

The survey was initiated in 2004 by members of the European Confederation for Medical Mycology (ECMM; ECMM Working Group on Zygomycosis) with the aim to prospectively collect cases of mucormycosis throughout Europe to obtain more information on demographics, organisms, risk factors, management, and outcome of this emerging fungal infection. The survey was based on the voluntary reporting of cases of all age categories by clinicians and laboratories via national coordinators to the ECMM study centre using a standardised, pseudonymized case report form (CRF). Submission of isolated fungal organisms or infected tissue specimen for further biological investigations was encouraged.

Data collected by the CRFs included demographic characteristics, underlying medical conditions and predisposing factors, use of antifungal agents prior to diagnosis, clinical presentation, methods of diagnosis, microbiological species identification, treatment, and outcome of the infection. Minimum data requirements for the inclusion of a case in this analysis were paediatric age, origin in Germany or Austria, information on demographics, underlying condition, clinical presentation, and diagnosis of mucormycosis. Proven mucormycosis was defined by compatible clinical and/or radiographic findings, conventional microbiological identification of the organism, and histopathological evidence in case of lung and paranasal sinus infection; and probable mucormycosis by compatible clinical and/or radiographic findings plus microscopic detection in biopsy specimens without microbiological identification of the organism.10 One case that was included on the basis of molecular detection of a zygomycete from bronchoalveolar lavage fluid (BAL) was classified as probable infection. All cases were reviewed and adjudicated as necessary by the national coordinator (AHG). Prior to the survey’s start, data collection, and data handling were approved by the Ethics Committee of the University Hospital Münster. Of note, the ECMM survey has been completed in the interim, and the combined analysis of all 230 adult and paediatric cases has been presented elsewhere.11

**Results**

Twelve cases of proven or probable mucormycosis from nine centres were reported between January 2004 and December 2008 (2004: 3; 2005: 4; 2006: 1; 2007: 3 and 2008: 1). The demographic and clinical characteristics of the 12 paediatric patients with mucormycosis are presented in Table 1.

Six patients were male, and six were female; the median age was 14.5 years (range: 0.1–17). The majority of patients (67%) was either treated for acute myeloid leukaemia (3), acute lymphatic leukaemia (2), non-Hodgkin lymphoma (1), and severe aplastic anaemia (1), or had received an allogeneic hematopoietic stem cell transplant (HSCT 1; during the aplastic phase). Other conditions included insulin-dependent diabetes mellitus (2), soft tissue trauma, and premature birth with lung hypoplasia and extracorporal membrane oxygenation (one patient each). With respect to potentially predisposing factors, six of 12 evaluable patients had received glucocorticosteroids, six of 11 were neutropenic (absolute neutrophil count <500 μl⁻¹), and seven of 10 had received broadspectrum antibacterial agents within 4 weeks prior to the diagnosis of the fungal infection; in addition, four of 12 evaluable patients were on antifungal therapy with either caspofungin or voriconazole at the time of diagnosis.

Mucormycosis was proven in nine, and probable in three cases. Isolates included *Lichtheimia* (syn. *Absidia pro parte, Mycocladus*) (5), *Rhizopus* (3) and *Mucor* (1) species. Infection was limited to the soft tissues in three cases, the lung in two cases, and an infected central thrombus in one case. Sinoorbital-cerebral disease was found in three cases, and pulmonary-mediastinal, pulmonary-cerebral and soft tissue-cerebral involvement in one case each. The sources of the isolate in cases of proven disease were the paranasal sinuses (*n* = 3), infected soft tissue (*n* = 3), lung tissue (*n* = 2), and an implanted catheter material (1). While in three patients, the diagnosis had been made within 24 h prior to death and no antifungal therapy was initiated, nine of the 12 patients were treated with antifungal agents (lipid formulations of amphotericin B, six; amphotericin B deoxycholate, two; consolidation/maintenance with posaconazole, four); four of these patients underwent surgical debridement or resection of affected tissue. Overall mortality was 67% (eight of 12 patients with follow-up). Three of the four survivors included the
patients with soft tissue infection who had received combined antifungal and surgical treatment; for non-
soft tissue infections, the outcome was particularly
dismal with 88% mortality.

Discussion

Invasive mucormycosis is a life-threatening infection in
children and neonates and has both similarities to and
differences from that in adults. Prematurity is a major
underlying factor among neonatal cases and the most
common reported manifestations of mucormycosis here
are gastrointestinal and cutaneous. In contrast, older
children and adults typically present with pulmonary
or sinuorbitocerebral patterns. Overall mortality is 64% in
neonates and 56% in children. Dissemination and
young age (<1 year) were independent risk factors for
death in children. Similar to adults, surgery combined
with antifungal therapy is a protective factor against
death in neonates and children.7–9 The vast majority of
adult patients with malignancy have pulmonary dis-
semination and mortality varies with the site of infection. Survival
is 70% for cases treated with antifungal therapy and
surgery compared with 3% for cases that were not
treated, 61% for cases treated with amphotericin B, and
57% for cases treated with surgery alone.4

In agreement with previously published risk factors
for mucormycosis,2,4–7,12 the underlying conditions in
our patients were haematological malignancies (58%).

Table 1 Demographic and clinical characteristics of 12 paediatric patients with mucormycosis.

<table>
<thead>
<tr>
<th>Patient ID/year</th>
<th>Age (years)</th>
<th>Underlying condition</th>
<th>Corticosteroids (yes/no)</th>
<th>Neutropenia (yes/no)</th>
<th>Antibacterials (yes/no)</th>
<th>Site of infection</th>
<th>Histopathology</th>
</tr>
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<tbody>
<tr>
<td>GE 13/2004</td>
<td>11</td>
<td>Severe aplastic anaemia</td>
<td>Yes</td>
<td>Yes</td>
<td>Yes</td>
<td>Rhinocerebral</td>
<td>Paranasal sinus</td>
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<tr>
<td>GE 18/2004</td>
<td>15</td>
<td>IDDM/ketoacidosis</td>
<td>No</td>
<td>No</td>
<td>No</td>
<td>Rhinocerebral</td>
<td>Paranasal sinus</td>
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<tr>
<td>AT 17/2004</td>
<td>17</td>
<td>AML/allo HSCT</td>
<td>Yes</td>
<td>Yes</td>
<td>Yes</td>
<td>Rhinocerebral</td>
<td>Paranasal sinus</td>
</tr>
<tr>
<td>GE 03/2005</td>
<td>14</td>
<td>T-ALL</td>
<td>Yes</td>
<td>Yes</td>
<td>Yes</td>
<td>Soft tissues</td>
<td>NA</td>
</tr>
<tr>
<td>GE 23/2005</td>
<td>16</td>
<td>T-ALL</td>
<td>Yes</td>
<td>No</td>
<td>NR</td>
<td>Soft tissues</td>
<td>NA</td>
</tr>
<tr>
<td>GE 26/2005</td>
<td>8</td>
<td>AML</td>
<td>No</td>
<td>NR</td>
<td>NR</td>
<td>Lung</td>
<td>Lung</td>
</tr>
<tr>
<td>GE 27/2007</td>
<td>10</td>
<td>Soft tissue trauma</td>
<td>No</td>
<td>No</td>
<td>No</td>
<td>Soft tissues</td>
<td>NA</td>
</tr>
<tr>
<td>GE 33/2007</td>
<td>0.1</td>
<td>Prematurity/lung hypoplasia</td>
<td>Yes</td>
<td>No</td>
<td>Yes</td>
<td>Thrombosed</td>
<td>NA</td>
</tr>
<tr>
<td>GE 38/2008</td>
<td>15</td>
<td>IDDM/ketoacidosis</td>
<td>No</td>
<td>No</td>
<td>No</td>
<td>Lung/mediastinum</td>
<td>Lung</td>
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</table>

<table>
<thead>
<tr>
<th>Patient ID/year</th>
<th>Microbial culture</th>
<th>Prior antifungals</th>
<th>Antifungal treatment</th>
<th>Antifungal agents</th>
<th>Surgical treatment</th>
<th>Outcome</th>
<th>Follow-up (days)</th>
</tr>
</thead>
<tbody>
<tr>
<td>GE 13/2004</td>
<td>Lichtheimia corymbifera</td>
<td>FCZ, CAS</td>
<td>Yes</td>
<td>LFAB</td>
<td>Debridement</td>
<td>Death</td>
<td>201</td>
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<tr>
<td>GE 18/2004</td>
<td>Rhizopus spp.</td>
<td>No</td>
<td>Yes</td>
<td>AMB, PCZ</td>
<td>No</td>
<td>Cure</td>
<td>609</td>
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<tr>
<td>AT 17/2004</td>
<td>Rhizopus oryzae</td>
<td>No</td>
<td>No</td>
<td>No</td>
<td>No</td>
<td>Death</td>
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</tr>
<tr>
<td>GE 03/2005</td>
<td>Mucor spp.</td>
<td>No</td>
<td>Yes</td>
<td>LFAB</td>
<td>Resection</td>
<td>Cure</td>
<td>20</td>
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<tr>
<td>GE 23/2005</td>
<td>Lichtheimia corymbifera</td>
<td>NR</td>
<td>Yes</td>
<td>AMB</td>
<td>Debridement</td>
<td>Cure</td>
<td>44</td>
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<td>GE 26/2005</td>
<td>Lichtheimia ramosa</td>
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<td>Yes</td>
<td>LFAB</td>
<td>NR</td>
<td>Unknown</td>
<td>NA</td>
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<tr>
<td>GE 27/2007</td>
<td>Lichtheimia corymbifera</td>
<td>No</td>
<td>Yes</td>
<td>LFAB, PCZ</td>
<td>Debridement</td>
<td>Cure</td>
<td>34</td>
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<tr>
<td>GE 33/2007</td>
<td>Rhizopus spp.</td>
<td>No</td>
<td>No</td>
<td>No</td>
<td>No</td>
<td>Death</td>
<td>1</td>
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<tr>
<td>GE 38/2008</td>
<td>Lichtheimia corymbifera</td>
<td>No</td>
<td>Yes</td>
<td>LFAB, PCZ</td>
<td>No</td>
<td>Death</td>
<td>7</td>
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<table>
<thead>
<tr>
<th>Patient ID/year</th>
<th>Microbial culture</th>
<th>Prior antifungals</th>
<th>Antifungal treatment</th>
<th>Antifungal agents</th>
<th>Surgical treatment</th>
<th>Outcome</th>
<th>Follow-up (days)</th>
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<tbody>
<tr>
<td>GE 30/2005</td>
<td>NA</td>
<td>VCZ</td>
<td>No</td>
<td>No</td>
<td>No</td>
<td>No</td>
<td>Death 1</td>
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<tr>
<td>GE 16/2006</td>
<td>NA</td>
<td>No</td>
<td>Yes</td>
<td>LAMB</td>
<td>No</td>
<td>No</td>
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<tr>
<td>AT 14/2007</td>
<td>Mucor by PCR</td>
<td>VCZ</td>
<td>Yes</td>
<td>LAMB, PCZ</td>
<td>No</td>
<td>Death</td>
<td>120</td>
</tr>
</tbody>
</table>

IDDM, insulin-dependent diabetes mellitus; AML, acute myeloid leukaemia; ALL, acute lymphatic leukaemia; NHL, non-Hodgkin lym-
phoma; HSCT, haematopoietic stem cell transplantation; PCR, polymerase chain reaction; ECMO, extracorporal membrane oxygenation;
FCZ, fluconazole; VCZ, voriconazole; PCZ, posaconazole; CAS, caspofungin; LFAB, lipid formulation of amphotericin B; AMB, amphotericin
B; NR, not reported/unknown; NA, not available/not done.
diabetes mellitus (17%), haematopoietic stem cell transplantation, soft tissue trauma and prematurity (8% each). While this study cannot yield conclusive information on incidence rates of invasive mucormycosis in different patient groups, frequency of registration may suggest epidemiological tendencies. In the largest subgroup of patients with haematological malignancies, the lung and brain could be confirmed as the typical site of infection, as reported previously. Disseminated disease was also associated with high mortality in our cohort (100%), whereas all patients with localised soft tissue trauma survived. Similar to larger, mostly literature-based case series, treatment with surgery and antifungal therapy was associated with a lower mortality in our cohort, when compared with cases that were not treated, or treated with antifungal medication alone. Cleyer, these statements are limited by the small number of patients. In previous reports on genus and species distribution Rhizopus spp., Mucor spp. and Cunninghamella bertholletiae have been mentioned as the most frequently isolated genus in studies from North America and Italy, whereas Lichtheimia corymbifera (syn. Absidia corymbifera, Mycocladus corymbifer), was the most commonly identified isolate in a registry study from central Europe and Asia. In agreement with this analysis, Lichtheimia was also the most commonly isolated agent of mucormycosis in our study, followed by Rhizopus spp. and Mucor spp.

In conclusion, mucormycosis is a life-threatening and often fatal disease in immunocompromised paediatric patients and a variety of underlying diseases. While these data cannot provide the full extent of disease burden of mucormycosis in paediatric patients in Germany or Austria, they reflect the continuing threat of these infections to immuno compromised patients and the need for improved diagnosis and management.

Acknowledgments

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Conflict of interest

AHG has served on the speaker’s bureau and as a consultant to Astellas Pharma, Cephalon, Gilead Sciences, Merck & Co., Pfizer, Schering-Plough, and Vicuron Pharmaceuticals. He has received research grants from Gilead Sciences and Merck & Co. TL has received grants from Gilead; is a consultant to Gilead, Merck, Sharp & Dohme and Schering-Plough, and served at the speakers’ bureau of Astellas, Gilead, Merck, Sharp & Dohme and Schering-Plough. All other authors: none to declare.

References