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Original article

Mucormycosis in Australia: contemporary epidemiology and outcomes

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ABSTRACT

Mucormycosis is the second most common cause of invasive mould infection and causes disease in diverse hosts, including those who are immuno-competent. We conducted a multicentre retrospective study of proven and probable cases of mucormycosis diagnosed between 2004–2012 to determine the epidemiology and outcome determinants in Australia. Seventy-four cases were identified (63 proven, 11 probable). The majority (54.1%) were caused by *Rhizopus* spp. Patients who sustained trauma were more likely to have non-*Rhizopus* infections relative to patients without trauma (OR 9.0, p 0.001, 95% CI 2.1–42.8). Haematological malignancy (48.6%), chemotherapy (42.9%), corticosteroids (52.7%), diabetes mellitus (27%) and trauma (22.9%) were the most common co-morbidities or risk factors. Rheumatological/autoimmune disorders occurred in nine (12.1%) instances. Eight (10.8%) cases had no underlying co-morbidity and were more likely to have associated trauma (7/8; 87.5% versus 10/66; 15.2%; p <0.001). Disseminated infection was common (39.2%). *Apophysomyces* spp. and *Saksenaea* spp. caused infection in immuno-competent hosts, most frequently associated with trauma and affected sites other than lung and sinuses. The 180-day mortality was 56.7%. The strongest predictors of mortality were

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mucormycete
mucormycosis
Rhizopus
Saksenaea
zygomycosis

rheumatological/autoimmune disorder (OR = 24.0, p 0.038 95% CI 1.2–481.4), haematological malignancy (OR = 7.7, p 0.001, 95% CI 2.3–25.2) and admission to intensive care unit (OR = 4.2, p 0.02, 95% CI 1.3–13.8). Most deaths occurred within one month. Thereafter we observed divergence in survival between the haematological and non-haematological populations (p 0.006). The mortality of mucormycosis remains particularly high in the immuno-compromised host. Underlying rheumatological/autoimmune disorders are a previously under-appreciated risk for infection and poor outcome. **K.J. Kennedy, CMI 2016;22:775**

Introduction

Infections caused by fungi of the order Mucorales are uncommon, but are significant for their aggressive nature, challenges in diagnosis and high mortality (40–100%) despite antifungal and surgical therapy [1–6]. The Mucorales are a diverse group of fungi associated with characteristic presentations according to underlying host conditions [1–3]. A significant proportion of infection also occurs in hosts with no apparent immune compromise, often in association with trauma [1–3,7,8].

The epidemiology of mucormycosis may be changing with the emergence of uncommon genera such as *Apophysomyces* [7,9], increasing numbers and breadth of immuno-compromised hosts [1] and outbreaks of infection following natural disasters and iatrogenic or other environmental exposure [7,10,11]. However, despite reports of rising incidence of mucormycosis [1,4,12], data on infection risks, treatment and outcomes are limited to case series and expert opinion. The epidemiology of mucormycosis varies between geographic regions [1–5,9,12], so knowledge of local patterns of disease is necessary to inform diagnosis and management. This multicentre study provides contemporary insights into the epidemiology, predisposing factors and determinants of outcomes of mucormycosis in Australia.

Materials and Methods

Study design

A retrospective multicentre, observational study of mucormycosis in adults was conducted across 15 Australian tertiary hospitals from 2004 to 2012 under the auspices of the Australia and New Zealand Mycoses Interest Group, and formed a substudy of a recently published analysis of invasive fungal disease (IFD) caused by non-*Aspergillus* moulds [13]. Institutional Human Research Ethics Committees approval was obtained at each site.

Collection of data

Cases were identified through a combination of pathology laboratory information systems, infectious diseases databases and hospital medical records coding [14]. A data review committee assessed each case for study inclusion. Only proven or probable infections were included. Patient demographics; co-morbid conditions (e.g. malignancy); predisposing factors for mucormycosis within the preceding 30 days of diagnosis (e.g. immunosuppressive therapies, trauma); site(s) of infection; microbiological and histological results; antifungal and other therapies; and clinical outcome at 30 and 180 days were collected.

Definitions

Proven or probable cases of mucormycosis were defined based on the European Organization for Research and Treatment of Cancer/Mycoses Study Group (EORTC/MSG) definitions for IFD [15]. However, in contrast to the EORTC/MSG criteria for assignment of probable IFD, host-specific criteria were not required.

Disseminated infection involved two or more non-contiguous sites or positive blood cultures. Gastrointestinal (GI) tissue infections included the intestinal tract, pancreas and liver. Prior antifungal use was defined as >7 days of treatment within the previous 30 days. Clinical outcome was assessed as all-cause mortality at 30 and 180 days.

Histopathological and microbiological examination

Clinical specimens were examined by experienced histopathologists at participating sites using local institutional protocols. The identity of cultured Mucorales was performed using standard phenotypic methods and, where available, characterized at a reference laboratory (Westmead Hospital or SA Pathology) by DNA sequencing targeting the internal transcribed spacer (ITS) regions or the D1/D2 regions of the 28S rRNA gene [16,17]. In some cases, panfungal PCR targeting the ITS 1 region was performed to identify Mucorales in histopathological specimens [18]. If species identification was not possible either by culture or by molecular methods, isolates were categorised either by genus or as 'unclassified Mucorales'.

Statistical analysis

Cases of 'unclassified Mucorales' were excluded when comparisons were made between genera. Categorical variables were compared using the χ^2 or Fishers exact test, and continuous variables by the Student's *t* test or Mann-Whitney *U* test where appropriate. Determinants of all-cause 30-day and 180-day mortality were examined by univariate and multivariate analysis. Backward, stepwise multivariate analysis was conducted with Firth's penalized-likelihood logistic regression due to the presence of complete separation of one variable. Variables with a univariate p value <0.20 were considered for inclusion in the model for multivariate analysis. Variables with p values ≤0.05 in a significant model with the largest penalized log likelihood were included within the final model. Kaplan–Meier survival analysis was performed for all-cause 180-day mortality and assessed by the log rank test. Calculations were computed using STATA (StataCorp. 2015. STATA Statistical Software: Release 14. College Station, TX).