

Disseminated mucormycosis in a paediatric patient: *Lichthemia corymbifera* successfully treated with combination antifungal therapy



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ABSTRACT

Mucormycosis is a severe fungal infection that largely affects immunocompromised individuals. It carries a high morbidity and mortality rate and is characterised by extensive angioinvasion and necrosis of host tissue. This case report details success in treating disseminated mucormycosis in a paediatric patient with an underlying haematological malignancy. Treatment included institution of combination antifungal therapy with liposomal amphotericin B and caspofungin, aggressive surgical debridement of infected tissue and reversal of underlying immunosuppression.

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1. Introduction

Mucormycosis is a life threatening infection caused by fungi of the order Mucorales [1–3]. These organisms are ubiquitous in the environment and are commonly found in decaying vegetation and soil [2]. Mucorales grow rapidly and release large numbers of spores that can become airborne and cause infection in humans when inhaled, ingested or introduced through a cutaneous route [2]. The disease largely affects immunocompromised individuals and those with diabetes mellitus, and is characterised by extensive angioinvasion, vessel thrombosis and necrosis of host tissue [2,3].

Epidemiological data for mucormycosis is conflicting and difficult to interpret given that mucormycosis is a rare infection and not a reportable disease [4,6]. Significant increases in the rates of mucormycosis have been observed among some adult patient groups classically at risk of opportunistic mould infections, including patients with haematological malignancies and those who have undergone a haemopoietic stem cell transplant (HSCT) or solid organ transplant [1,12]. Smaller epidemiological studies in paediatric patients have not shown the same trends [13]. Sinus and pulmonary infections are the most common clinical syndromes reported in adults, however cutaneous and gastrointestinal infections are the most commonly reported amongst paediatric populations [4,5].

Mortality rates for disseminated mucormycosis are unacceptably high and approach almost one hundred per cent, highlighting the critical need for new treatment approaches [4–6]. There has been considerable interest in studying novel combinations of antifungal agents, to determine if improved outcomes might be achieved [7–9]. This case report details success in treating a paediatric patient with disseminated mucormycosis using four important strategies for management, including: (1) early diagnosis, (2) reversal of underlying immunosuppression, (3) rapid initiation of effective antifungal therapy and (4) aggressive surgical debridement of infected tissue [1,3].

Liposomal amphotericin B (L-AMB) and echinocandins appear to be the most promising candidates for effective combination antifungal therapy used to treat mucormycosis, despite echinocandins having no activity against fungi that cause mucormycosis in standard in vitro susceptibility testing [7–9]. This postulation is instead based on pharmacological studies, murine models, observational data and the availability of these agents in the parenteral form [8,9,11].

2. Case

An 11 year old girl presented with a history of one week of lethargy and one day of abdominal pain and she was admitted to the Oncology Unit at The Women's and Children's Hospital (day 0). She was in the delayed intensification maintenance phase of treatment for T-cell acute lymphoblastic leukaemia (T-ALL) and had been neutropenic for eight days prior to the admission. Examination revealed generalised abdominal tenderness, without

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signs of a surgical abdomen. Initial investigations showed a pancytopenia with a neutrophil count of $0.03 \times 10^9/L$, mildly elevated liver function tests, a normal lipase and an elevated C-reactive protein of 115 mg/L. A computer tomography (CT) of her chest, abdomen and pelvis on day 1 and 2 showed a diffuse ground glass opacity in the right lower lobe of the lung and opacification of the right major pulmonary arteries and veins, in keeping with a pulmonary artery and venous thrombosis (Fig. 1). A lesion in the head of the pancreas was also identified (Fig. 2). L-AMB was commenced on day 2 at 5 mg/kg/day and all chemotherapy was placed on hold. Neutrophil count recovery was achieved, without the use of hematopoietic growth factors, by day 3 of the admission and fevers emerged during this time.

The patient had ongoing abdominal pain and further imaging showed an inflamed appendix. An appendectomy was performed on day 6 and the histology from tissue samples showed fungal elements confirming a zygomycete (Fig. 3), however there was no growth from fungal cultures.

On day 7, repeat imaging revealed further lesions in the medial aspect of the right kidney (Fig. 4) and in the left occipital lobe of the brain (Fig. 5), as well as rapid growth of the preexisting lesions

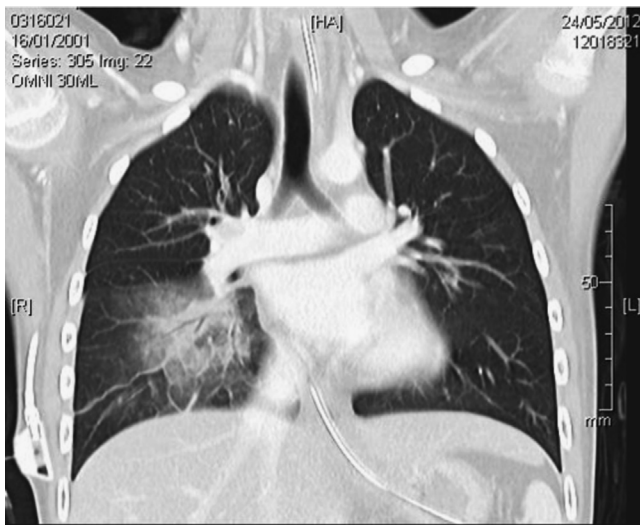


Fig. 1. CT pulmonary angiogram shows diffuse ground glass opacity in right lower lobe of the lung with some interlobar thickening. There is opacification of the major pulmonary arteries and veins in keeping with a right pulmonary artery and vein thrombosis.



Fig. 2. CT scan of the abdomen shows a hypodense lesion in the uncinate process of the head of the pancreas.

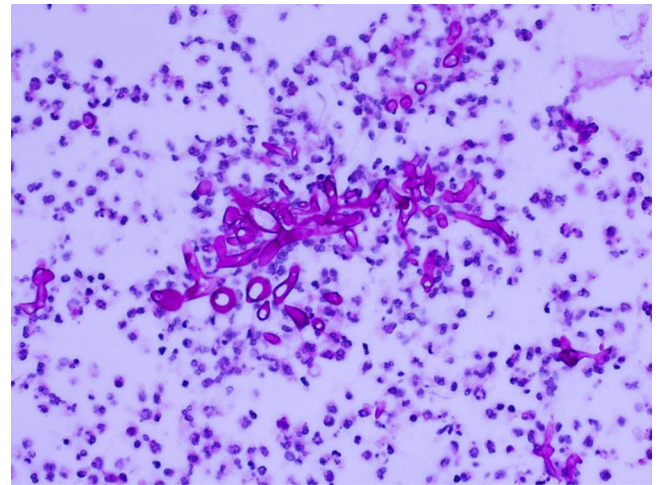


Fig. 3. Hematoxylin and eosin stain on a tissue sample from the appendix. The hyphae are broad (6 to 25 micrometre wide), thin-walled and pleomorphic, with sparsely septated hyphae. Branches arise haphazardly, often at right angles to the parent hyphae. Because the hyphae have little structural stability, they are often folded, twisted, wrinkled, or collapsed.

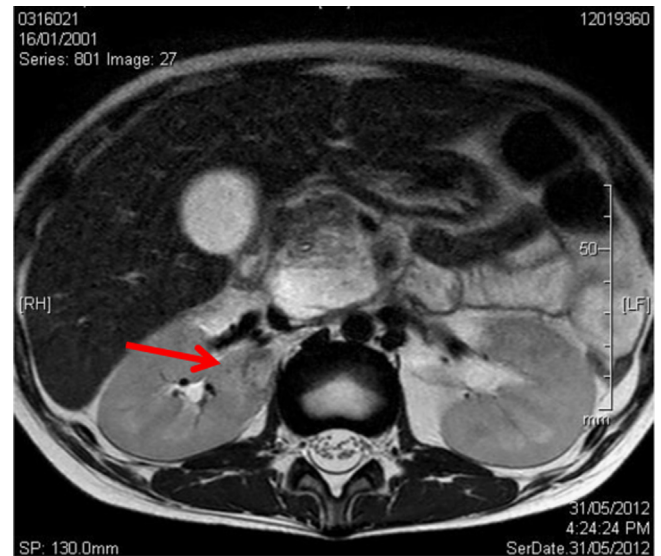


Fig. 4. MRI of the abdomen shows a non-enhancing lesion centrally in the medial aspect of the mid-pole of the right kidney.

in the lung and pancreas. On day 11, combination antifungal therapy was initiated, with the addition of caspofungin, at a loading dose of $70 \text{ mg/m}^2/\text{day}$, continuing at $50 \text{ mg/m}^2/\text{day}$ and L-AMB was continued at a higher dose of 10 mg/kg/day .

Over the following seven weeks the patient was continued on combination antifungal therapy and aggressive surgical management was implemented. This involved multiple operations, that were aimed at resecting affected tissue and controlling two potentially life threatening haemorrhages. Thoracotomy and right lower lobectomy of the lung were performed on day 10, when the patient developed life-threatening haemoptysis. The lung specimens grew mould identified as *Lichtheimia corymbifera* (Fig. 6). A craniotomy and drainage of the left occipital brain abscess and a right nephrectomy were performed, on day 15 and 17, respectively. As a precaution a sphenoidotomy and biopsies of the sinuses were performed, which yielded no growth from fungal cultures.

Complete excision of the pancreatic lesion was an operation that was deemed to carry high surgical risks for this patient.

Alternatively percutaneous drainage of the lesion was performed and a peripancreatic drain was inserted. A pancreatobiliary stent was later inserted to alleviate biliary tract obstruction due to

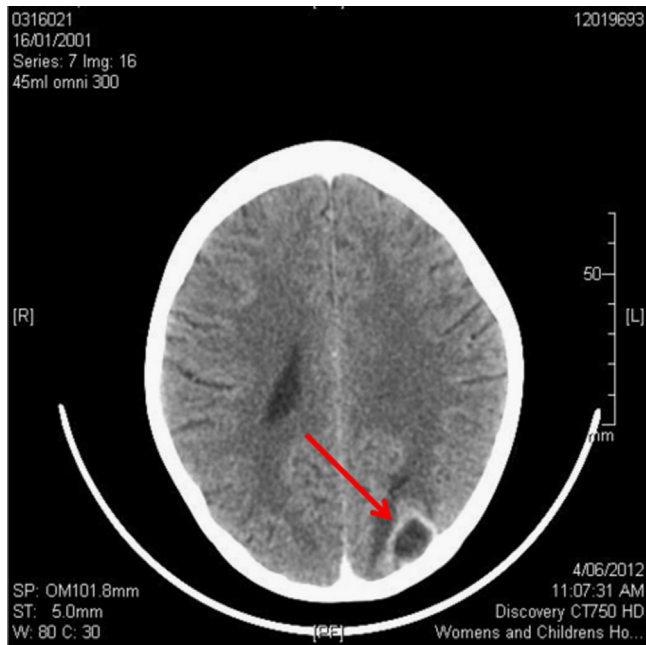


Fig. 5. CT scan with contrast shows an irregular hypodense ring-enhancing lesion in the subcortical region of the left posterior occipital lobe of the brain.

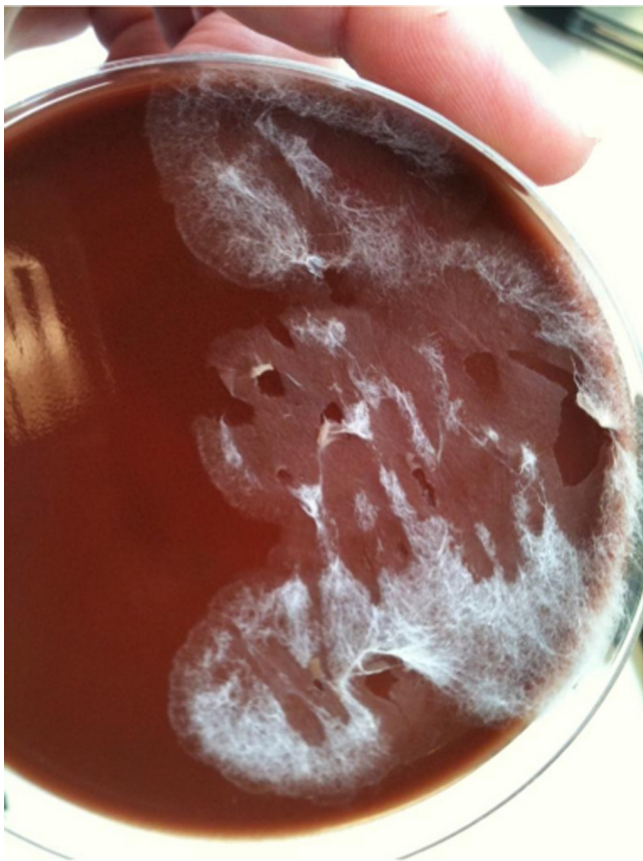


Fig. 6. Malt extract agar plate shows culture growth of mould from lung tissue specimens. The colonies are white and grey in colour and contain cottony aerial mycelium. Identification of the mould as *Lichtheimia Corymbifera* was based on microscopic morphological features such as branched sporangiophores, internodal rhizoids, funnel-shaped apophyses and dome-shaped columella.

compression from the surrounding pancreatic lesion. On day 34, the patient then haemorrhaged from the peripancreatic drain with resulting haemodynamic instability. A mesenteric angiogram revealed a mesenteric artery aneurysm and a stent was inserted to control the bleeding. On day 46, cholecystectomy and hepaticoduodenostomy were performed for persistent biliary leakage from the common bile duct.

After 8 weeks the patient remained stable and was recommenced on chemotherapy with a modified maintenance regime to avoid neutropenia. The caspofungin was then ceased and the patient was continued on treatment doses of L-AMB (10 mg/kg/day) for a total duration of 3 months. This regime was then stepped down to twice-weekly L-AMB infusions (5 mg/kg/day on Mondays and Thursdays). An alternative antifungal for step-down therapy was oral posaconazole, however this could not be used initially due to suboptimal drug serum levels, secondary to poor oral intake.

The patient then developed significant renal impairment after 10 months, which was thought to be of multifactorial aetiology. Oral posaconazole (250 mg QID via a nasogastric tube) was then re-trialled successfully and the L-AMB was ceased. Adequate serum drug levels of posaconazole were achieved, aiming for a trough serum concentration of greater than 1.2 mg/L. The patient will continue on oral posaconazole until treatment for T-ALL is complete. Currently two years on from the initial diagnosis, the patient has no evidence of recurrence of mucormycosis and remains in remission for T-ALL.

3. Discussion

As detailed in this case, the main risk factor for the patient developing mucormycosis was prolonged, profound neutropenia, which creates defects in phagocytic activity allowing unimpeded growth of moulds [2]. Patients with prolonged neutropenia, more commonly develop pulmonary mucormycosis and are at the highest risk of going on to develop disseminated forms [6]. Achieving neutrophil count recovery as early as possible is therefore critical in the management of mucormycosis and was a major factor contributing to a successful outcome for this patient [14]. Immunosuppressive medications, particularly corticosteroids, should be administered at reduced doses or preferably stopped if possible [1]. Granulocyte colony-stimulating factor transfusions can provide additional support for persistently neutropenic patients, until recovery from neutropenia is achieved [10].

Making an early diagnosis to facilitate rapid initiation of antifungal therapy, along with extensive and aggressive surgical debridement of involved tissues, is crucial for the management of mucormycosis [15]. Multiple studies have found surgery to be an independent variable for a favourable outcome in patients with mucormycosis [4,5,10]. The rapid progression of this infection should be explained to the treating surgical teams involved, who may otherwise be reluctant to perform extensive debridement. Treatment delay is associated with increased mortality and early diagnosis often depends on a high index of clinical suspicion [15]. Clinical suspicion must be heightened for patients with predisposing risk factors for mucormycosis, including those with; diabetes mellitus, haematological malignancies, HSCT and solid organ transplant, iron overload, prematurity, trauma or burns, injecting drug use and malnutrition [1,5].

Early diagnosis is difficult, relying on identification of organisms in tissue by microscopy and culture [15]. Invasive testing must be pursued early for patients with signs, symptoms and risk factors for fungal infections and those with progressive disease despite treatment covering most fungal pathogens [15,16]. It is important to note that it is often difficult to grow agents of

mucormycosis from a clinical specimen. The grinding of clinical specimens can cause excessive damage to the hyphae, preventing growth in culture mediums [15]. Communication to the treating teams regarding the handling of the specimen is therefore paramount for isolation of the fungus [16].

L-AMB is the current first line antifungal agent for the treatment of mucormycosis [17]. Multiple case series have found L-AMB to be substantially more effective than amphotericin B deoxycholate for the treatment of mucormycosis [10]. Lipid formulations of amphotericin B are significantly less nephrotoxic and can be safely administered at higher doses than non-lipid formulations [10]. The optimal dosage of L-AMB that should be administered to treat mucormycosis has not yet been studied adequately [1]. Some clinicians will increase the dose up to 10 mg/kg/day, particularly for patients with central nervous system involvement (CNS) given the low penetration of polyenes into the CNS [1].

There are some proposed mechanisms as to how combination antifungal therapy with polyene-echinocandins possibly improves the treatment of mucormycosis. These include (1) disruption of beta-glucan cross-linking of the cell wall of the fungi, leading to enhanced polyene delivery to the cell membrane, (2) altered virulence of the fungus and (3) enhanced host response to the fungus [8]. In neutropenic mice with disseminated mucormycosis, combination therapy with L-AMB plus an echinocandin markedly improved survival compared with monotherapy with L-AMB [11]. Furthermore polyene-caspofungin antifungal combination therapy was associated with significantly improved survival for patients with rhino-orbito-cerebral mucormycosis compared with polyene monotherapy (100% vs. 45%; $P=0.02$) [9]. This study was limited by a small sample size ($n=20$), predominance of adult diabetic patients and few neutropenic patients (16%) and the study was retrospective in nature [9]. It is evident that randomised controlled phase three clinical trials are needed to determine whether combination therapy is superior to monotherapy [8].

The difficulties of achieving adequate serum drug levels on oral posaconazole are highlighted in this case and became critically important when the patient developed severe renal impairment whilst on L-AMB. Posaconazole should not be given as initial therapy, but can be used as step-down or salvage therapy [1,18]. Patients can be switched from L-AMB to oral posaconazole once a favourable clinical response has been achieved, which usually takes many weeks [18]. Antifungal therapy should continue until there is clinical as well as radiological resolution and until reversal of underlying immunosuppression has been achieved [16]. An important strategy used in this case was the overlapping of antifungals, enabling assessment of posaconazole absorption with drug levels, whilst the patient was still on L-AMB. Intravenous posaconazole may become available for paediatric patients in the future, which would avoid the need for a high dietary intake of lipids to achieve adequate serum drug levels [18].

Conflict of interest

There are no conflicts of interest to declare.

Acknowledgements

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