Case report

Mucormycosis – deadly disease and deadly treatment

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Introduction

Mucormycosis is an emerging angioinvasive mycosis caused by the filamentous fungi of the Mucorales order of the class of Zygomycetes. The clinical spectrum extends from cutaneous infection to rhinocerebral, and sino-pulmonary to frequently fatal disseminated infections, especially in immunocompromised hosts. Life-saving measures include surgical debridement, high-dose amphotericin B and treatment of the underlying immuno-deficiency. Amphotericin B is the most effective antifungal therapy for mucormycosis, but has potentially fatal adverse effects. We report a patient with rhinocerebral mucormycosis who unexpectedly died while improving on treatment to highlight the potentially fatal adverse effects of amphotericin B.

Case report

A 60-year-old man with type 2 diabetes mellitus and hypertension for 10 years complicated with non-proliferative diabetic retinopathy and diabetic nephro-pathy, presented with left-sided facial paralysis of 6 hours duration. He had developed dull intermittent left-sided maxillary and temporal facial pain and numbness associated with malaise and anorexia one month prior to presentation. There was no history of fever, family or contact history of tuberculosis. His past glycaemic control was poor.

On examination, he was noted to have a partial 3rd nerve palsy with mild pupillary dilatation, a lower motor neuron facial nerve palsy, and a palatal palsy on the left. Sensory loss was demonstrable in the left trigeminal territory with involvement of the ophthalmic, maxillary and mandibular divisions. Optic fundi showed evidence of non-proliferative diabetic retinopathy. Rest of the systems and general examination was unremarkable. His pulse rate was regular and blood pressure was 170/90 mmHg. After admission to hospital the patient developed 6th and 8th nerve palsies on the left while the initial 3rd, 5th and 7th nerve palsies worsened.

His white cell count was 16,900/cumm with 80% neutrophils. Inflammatory markers were elevated with an ESR of 136 mm/h and a CRP of 96 mg/dl. Renal and liver function tests were normal. Non-contrast enchanced cranial computerized tomography scan was normal apart for opacities in the left ethmoid and maxillary sinuses. Cerebrospinal fluid analysis was normal. Gadolinium-enhanced magnetic resonance imaging of the brain demonstrated contrast enhancing invasive lesions in the left ethmoid and maxillary sinuses eroding into the surrounding bones (Figure 1). Nasal endoscopy found significant debris in the left ethmoidal sinus and gram stain was positive for fungal hyphae.

The patient underwent surgical debridement of the left ethmoid and maxillary sinuses and was commenced on amphotericin B. Over the next days to weeks, the patient demonstrated progressive clinical improvement with resolution of cranial nerve palsies, return of appetite and feeling generally well. During the course of treatment with amphotericin B, the patient developed a transient rise in serum creatinine, which stabilized with adequate hydration and conversion to amphotericin B lipid complex preparation. The serum potassium level remained normal and there was no evidence of renal tubular acidosis. However, he developed hypomagnesaemia with a serum magnesium level of 0.5 mmol/l (reference range 0.7-1.5mmol/l), which was corrected with intravenous magnesium sulphate. Serum magnesium and calcium levels were tested every third day of amphotericin B treatment. However, this monitoring could not be con-tinued in the third week of treatment due to the unavailability of reagents. Despite neurological and general improvement, the patient developed torsades de pointes and subsequent refractory monomorphic ventricular tachycardia and died 21 days after com-mencing amphotericin B.

Discussion

We describe a patient with mucormycosis who made a good recovery due to early diagnosis and initiation of appropriate treatment, but died possibly as a result of amphotericin B (AmB) related toxicity.

Although AmB is the only pharmacological pre-paration licensed for the management of mucormycosis it has an unfavorable adverse effect profile, including infusion related adverse effects and renal toxicity. The spectrum of renal toxicity encompasses acute kidney injury, interstitial nephritis, renal potassium and magnesium wasting and renal tubular acidosis. Cardiac toxicity with ventricular arrhythmias and bradycardia is reported in adults with preexisting cardiac disease,

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even when administered in conventional dosages and infusion rates. Reports of arrhythmias in patients with normal concentration of potassium and magnesium who were given AmB intravenously suggest that it may be directly cardiotoxic[1]. Nephrotoxicity is notably low with the lipid formulations of AmB[2].

Our patient had extensive sinus disease with cranial nerve involvement and diabetes as poor prognostic features, but had an initial good recovery with surgical intervention and AmB therapy. Nephrotoxicity was noted with AmB but was non-progressive with the use of the lipid complex preparation of AmB. Hypomagnesaemia associated with AmB therapy is common by the second week of therapy and maximal by the fourth week of treatment with AmB. The hypomagnesemia is usually mild, but a severe decrease in plasma magnesium levels requiring magnesium supplements may develop in some patients[3]. It is curious that our patient developed significant hypomagnesemia relatively early during therapy. The fatal complication of refractory ventricular arrhythmia and torsades de pointes are postulated to have occurred as a consequence of hypomagnesemia as well as the direct cardiotoxic effect of the drug. Inability to measure magnesium levels as recommended during treatment due to resource limitation is likely to have contributed to the mortality of this patient.

Mucormycosis is potentially fatal, especially in patients with disseminated disease and in those with central nervous system involvement. Recent estimates of mortality range from 44 -80% (4-6) with variation noted based on the extent of involvement, comorbidities and duration of response to therapy. Factors such as prolonged neutropenia or underlying hematological malignancy are also noted to predispose to mortality[7]. Furthermore, the disease is gaining increasing significance especially in the developing world due to its predilection in patients with diabetes mellitus. Data from a study in a tertiary care center in India demonstrate that 74% of patients with mucormycosis had uncontrolled diabetes[8]. The noted mortality of the disease among patients with diabetes mellitus is 40% with 80% of deaths occurring in low- to middle-income populations[9].

Conclusions

Mucormycosis is a disease with high mortality but the drug treatment of the disease is equally deadly as highlighted in our case. The need for stringent cardiometabolic monitoring during treatment with amphotericin B cannot be more emphasized.

References

1. Burke D, Lal R, Finkel KW, et al. Acute amphotericin B overdose. *Ann Pharmacother* 2006; **40**: 2254-9.
2. Luber AD, Maa L, Lam M, Guglielmo BJ. Risk factors for amphotericin B induced nephrotoxicity. *J Antimicrob Chemother* 1999; **43**: 267-71.
3. Barton CH, Palh M, Vaziri ND, Cesario T. Renal magnesium wasting associated with amphotericin B therapy. *Am J Med* 1984; **77**: 471-4.
4. Roden MM, Zaoutis TE, Buchanan WL, et al. Epidemiology and outcome of zygomycosis: a review of 929 reported cases. *Clin Infect Dis.* 2005; **41**: 634-53.
5. Spellberg B, Kontoyiannis DP, Fredricks D, et al. Risk factors for mortality in patients with mucormycosis. *Med Mycol.* 2012; **50**: 611-8.
6. Lanternier F, Dannaoui E, Morizot G, et al. French Mycosis Study Group. A global analysis of mucormycosis in France: the RetroZygo Study (2005-2007) *Clin Infect* Dis. 2012; **54** (Suppl 1): S35-S43.
7. Singh N, Aguado JM, Bonatti H, et al. Zygomycosis in solid organ transplant recipients: a prospective, matched case-control study to assess risks for disease and outcome. *J Infect Dis.* 2009; **200**: 1002-11.
8. Chakrabarti A, Das A, Mandal J, et al. The rising trend of invasive mucormycosis in patients with uncontrolled diabetes mellitus. *Med Mycol.* 2006; **44**: 335-42.
9. Arce-Salinas CA, Pe´rez-Silva E. Mucormycosis complications in systemic lupus erythematosus. *Lupus* 2010; **19**: 985-8.