Case Report

Cerebral aspergillosis: long term efficacy and safety of liposomal amphotericin B in kidney transplant

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Introduction

Opportunistic fungal infections are an important cause of morbidity and mortality in immunodepressed patients especially organ transplant recipients [1–3]. Aspergillus fumigatus is present in the environment worldwide and its invasive cerebral localization is complicated by a high mortality rate (more than 95%) in immunosuppressed hosts [4].

Case

M.L., a 52-year-old Italian male patient underwent a cadaveric transplant with a six antigen matched kidney at Mount Sinai Hospital, New York City, USA, in October 1995. Early post-operatively the patient was diagnosed with oesophageal CMV and was treated with ganciclovir. During the treatment he developed pneumonia, consistent with CMV and required mechanical ventilation. He suffered a long course with several respiratory decompensations and ganciclovir was continued. In February 1996 the patient had a subtle mental status change with seizure; positive sputum and skin lesions for Aspergillus were demonstrated. Chest X-ray was essentially normal, lumbar puncture was negative, radiographs of the sinus were not performed.

A cranial MRI showed two small frontal lesions, which were worked to rule out infection versus neoplasm. He had a Thallium scan which ruled out neoplasm and the left-sided lesion was biopsied and proved to be Aspergillus. He was then started on amphotericin B (60 mg QD) to cover for Aspergillus, dilantin and phenobarbital (serum creatinine 1.1 mg/dl); immunosuppression was reduced for some weeks. The patient’s initial therapy with amphotericin B deoxycholate (20 doses of 1.2 g) was then changed to liposomal amphotericin B (300 mg QD, then 300 mg qOD) for adverse effects (fever and chills) and at least 2–3 disseminated skin lesions, where Aspergillus was clearly evident with biopsy. The following MRI showed no other lesions and a decrease in size of the frontal abscess; immunosuppressive therapy was again started at a full dosage. He was discharged from Mount Sinai Hospital in July 1996 and returned to Italy. In the following months he continued liposomal amphotericin B (300 mg every other day) and underwent further cranial MRI. The CNS lesion showed no change in size with sclerotic evolution and the patient was re-evaluated for a second surgical procedure. In December 1996 he was submitted to a surgical resection.

Fig. 1. Cranial MRI, executed on February 14, 1997, depicts complete absence of the second frontal fungal abscess with gial reaction around the old lesion and meningeal uptake of the contrast medium.
of the CNS lesion (Figure 1). The post-operative biopsy exhibited fragments of neural tissue with moderate reactive gliosis; the edge of one fragment of pia-arachnoid showed thickening with some lymphocytes and macrophages. Liposomal amphotericin B was reduced and then stopped in the first days of January 1997. He had been treated for almost 10 months with liposomal amphotericin B with a cumulative dosage of 42.88 g (41.68 g + 1.2 g). During the course of anti-fungal treatment renal graft function was unmodified, immunosuppressive regimen was continued and nephrotrophic manifestations (especially hypokalaemia) were not seen (serum creatinine 1.1 mg/dl, creatinine clearance 74 ml/min at the end of therapy).

Discussion

Commonly the most clinical pattern of aspergillosis is the onset of unremitting fever and pulmonary infiltrates on chest X-ray.

In addition, aspergillosis of the central nervous system is a rare, but well-described disease in immunosuppressed patients [1]. The predominantly clinical symptoms of the CNS aspergillosis are focal neurological deficits particularly hemiparesis. Seizures are uncommon and headaches were absent in both immunosuppressed and immunocompetent patients. Early detection and aggressive combined treatment with extensive neurosurgical approach and amphotericin B is mandatory for survival [4].

Conventional amphotericin B, commonly prescribed in serious fungal infections, is limited by its important nephrotrophic manifestations [5,6]. A number of recent studies showed that conventional amphotericin B alters cell membrane permeability and as a consequence alters tubular and vascular smooth muscle cell function, leading to tubular transport defects and vasoconstriction. Reduced renal blood flow appears to play an important role in the amphotericin B induced-reduction GFR and recurrent ischaemia may be the basis of permanent structural nephrotrophic effects [5].

Liposomal amphotericin B is a new preparation that allows high safety with less toxicity than the standard formulation [7]. The formulation of an emulsion of amphotericin B in lipid may provide a protective action based on altering the affinity of amphotericin B for mammalian cell membranes, while efficacy against fungal cells is preserved [5]. Early studies showed its efficacy in candidosis and aspergillosis and that doses of up to 5 mg/kg could be used [8].

Adverse events were rare with mainly low back pain, dyspnea and low potassium; lack of renal and liver toxicity or anaemia were confirmed in subsequent studies [9–12].

To our knowledge, our own patient is only the third survivor to be described after CNS aspergillosis in a renal transplant recipient; a past review of the literature reported 25 survivors of invasive CNS aspergillosis in immunosuppressed patients [13–15].

In our case report, long term treatment with liposomal amphotericin B was associated with no further progression of the existing cerebral lesion, no other development of cerebral abscesses and sclerotic evolution of the old lesion. No new fungal skin lesions were described during the treatment with AmBisome. In addition, no data were reported in literature about patients treated with such a high dose of liposomal amphotericin B and for such a long period.

Liposomal amphotericin B showed a good safety and efficacy at high doses with no nephrotrophic or other toxic manifestations. Renal graft function was still unchanged for all the time of treatment with no increment of serum creatinine from the baseline and creatinine clearance more than 70 ml/min. A rare low back pain was reported during i.v. infusion of the drug.

In conclusion high doses of liposomal amphotericin B could represent a new, important advance in the treatment of invasive aspergillosis in immunodepressed hosts. Because of its availability and safety, long term administration is possible in renal transplants without nephrotrophic effects also at high cumulative doses.

References

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