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Disseminated Invasive Aspergillosis with Cerebral Involvement Successfully Treated with Caspofungin and Voriconazole

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Abstract

We describe a case of cerebral aspergillosis which was successfully treated with a combination of caspofungin and voriconazole. The patient remains in remission 18 months after stopping antifungal treatment. We discuss primary and salvage therapy of invasive aspergillosis with focus on cerebral involvement. Since historical data showed a fatal outcome in most cases, amphotericin B does not cross the blood brain barrier while voriconazole does, we chose a combination of voriconazole plus caspofungin as primary therapy.

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Introduction

Invasive Aspergillosis (IA) is a serious infectious complication in patients with bone marrow transplantation, haematological malignancies and after solid organ transplantation. Immunocompromised individuals due to burns, cancer, immunosuppressive therapy, especially corticosteroids are also at high risk.

IA remains an important cause of morbidity and mortality despite therapeutic interventions in this patient population. Cerebral Aspergillosis (CA) accounts for about 10% of all cases of IA [1]. The outcome of CA is dismal with mortality rates exceeding 90% [2]. Historically standard treatment was amphotericin B deoxycholate, which could be replaced by lipid-based preparations of amphotericin B in cases of toxicity or major side effects [3].

Voriconazole, a new broad spectrum triazole showed promising clinical responses in patients with pulmonary or tracheobronchial IA [4]. Since 2002, voriconazole is first line therapy of IA [5]. Caspofungin, a novel echinocandin, is a promising drug for salvage therapy in patients with IA whose disease is refractory to or who are intolerant to conventional Amphotericin B [6]. Whether these novel agents could be used in combination with or in addition to conventional or liposomal amphotericin B, needs to be determined.

Case Report

A 43-year-old caucasian cook was treated in a referral hospital with oral steroids for an acute steatohepatitis in a cirrhotic liver due to alcohol consumption and being overweight. One month later he developed ascites. After 2 months, he was referred to the emergency room in a coma. No metabolic alteration was found, although hepatic encephalopathy was not excluded by an EEG. A contrast-enhanced brain CT scan found multiple supra- and infratentorial ring-enhanced lesions suspicious for abscesses. In addition, a lesion in the right upper lung lobe was detected. The largest lesion in the cerebellum was neurosurgically removed and pathological examination showed septated hyphae. Cultures for bacteria and fungi remained negative. Broad spectrum fungal PCR in the surgically removed specimen identified *Aspergillus fumigatus* as the causative agent for the abcesses and a diagnosis of IA with brain abscesses was made [7]. The primary focus was most likely the lung lesion, although this suggestion was not proved by invasive procedures. Liver cirrhosis in Child Pugh Score C and the high dose steroid treatment for 2 months were identified as potential risk factors.

Combination therapy with caspofungin, 50 mg (after a single loading dose of 70 mg) intravenous and voriconazole, 50 mg twice daily, orally, was started. The voriconazole dose was empirically reduced because of the decompensated liver cirrhosis. The patient's condition improved within days and he suffered no side effects. He could be discharged after two and a half weeks without neurologic sequelae. After 1 month of combination treatment, he experienced an epileptic seizure, even though CT scans showed smaller brain lesions and no edema. The etiology of this seizure remained unclear. After starting antiepileptic treatment with phenytoin, no additional seizure occurred. Liver function improved successively to a Child Pugh score A. Therefore we increased the voriconazole dosage step by step under close monitoring of the drug level to finally 200 mg twice a day. After 8 months of taking this combination therapy (caspofungin 50 mg intravenous once a day and voriconazole 200 mg

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twice a day), a brain MRI showed two small residual supratentorial lesions of 6 mm and 8 mm, respectively and a defect after surgery, in the cerebellum. On CT scan, no ring enhancement was observed. The lesions were therefore considered to be non vital and caspofungin was stopped. Voriconazole was continued for an additional 16 months (2 years in total). During an 18 months follow up after stopping voriconazole, the patient did well and started a second education as a nutrition consultant. One year after stopping the anti-epileptic drugs and with a normal EEG, the neurologist allowed him to drive a car again. Liver function remains stable with an INR of 1.3 and an albumin of 36 g/l resulting in a Child Pugh score A.

The costs for the two anti-fungals amounted to approximately 230,000 Euros. The patient's medical insurance denied coverage arguing, that combination treatment of caspofungin/voriconazole is still experimental and we should have been using amphotericin B initially. The case went to court and finally the insurance company had to pay for the cost of both drugs.

Discussion

We believe that fatal outcome of cerebral IA can be avoided in the era of new antifungals. Successful treatment of CA with voriconazole was first reported in 1997 in a patient with acute leukaemia [8]. Selected cases of CA treated with voriconazole in children [9] and adults [10] were reported. In cases of pulmonary aspergillosis voriconazole usage brought a favorable outcome after failure of amphotericin B [11]. Limited efficacy of amphotericin B and itroconazole in patients with CA is explained by their poor penetration into cerebrospinal fluid (CSF). High drug concentrations of voriconazole in CSF of guinea pigs and immunocompromised patients have been reported [12], which may explain favourable outcome of CA in patients treated with voriconazole.

Caspofungin is an effective, yet less toxic, alternative to amphotericin B for the treatment of invasive candidiasis [13]. In combination with liposomal amphotericin B, caspofungin promises encouraging outcome as primary or salvage therapy against IA in high-risk patients with haematologic malignancies [14]. The potential benefit of caspofungin in treating central nervous system infection due to *Aspergillus* spp. was demonstrated in a patient with a brain abscess due to aspergillus, who was successfully treated with caspofungin monotherapy after developing nephrotoxicity under treatment for 13 days with amphotericin B [15].

Because of different mechanisms of action, the absence of cross-toxicity and by enhancing each others efficacy, the combination of caspofungin and voriconazole could be a promising alternative. Laboratory findings [16] and studies in animal models [17] confirmed a synergic interaction between these two agents. The first case of a successful treatment of CA with caspofungin/voriconazole was described in 2003 after failure of amphotericin B based standard treatment [18]. One small case serie (five patients) with favorable results was published in abstract form [19].

Our case shows an excellent outcome with complete recovery even 18 months after stopping the antifungal drugs. Because the mortality of CA approaches 100%, we started our patient directly on the combination therapy of caspofungin/voriconazole avoiding the mostly unsuccessful use of amphotericin B with its poor penetration into the CSF. This is supported by the data of *Marr* et al. [20]. In their retrospective evaluation of patients with IA after failing amphotericin B, the combination of caspofungin/voriconazole showed a significant survival benefit after 3 months compared to voriconazole monotherapy.

In our case, voriconazole was initially very low dosed. This empirical reduction gives us some doubts about the therapeutic effect at the very beginning of this case and underlines the importance of administration of the synergistic caspofungin.

Therefore, in cases of IA with cerebral involvement, the combination therapy of caspofungin and voriconazole might be an option. Further trials are needed to determine its efficacy and to provide data about penetration into CSF.

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