Aerosolized amphotericin B lipid complex and invasive pulmonary aspergillosis: a case report

Amfotericina B in complessi lipidici aerosolizzata e aspergillosi polmonare invasiva: un caso clinico

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INTRODUCTION

Aspergillus species are saprophytic and widespread fungi responsible mainly for lung infections in predisposed subjects who inhale airborne spores. Pulmonary aspergillosis assumes different forms changing with the immunological characteristics of the host: invasive pulmonary aspergillosis (IPA) is potentially fatal and in the last few decades it has become one of the most serious infections in patients with prolonged neutropenia, allogenic stem cell transplant (HSCT), solid organ transplant (SOT) and receiving high-dose corticosteroids [1]. In invasive aspergillosis voriconazole proves to be more effective than amphotericin B deoxycholate (D-AMB) and it is considered the best standard therapy. Lipid amphotericin formulations (liposomal, L-AMB, and lipid complex, ABLC) represent an alternative treatment. The rescue therapy includes posaconazole, itraconazole and caspofungin [2]. The recovery of immunocompetence and surgical therapy when possible are fundamental to control the infection [3]. Problems of efficacy, safety, interactions and costs explain the growing interest in new strategic therapies. In the circle of innovative therapies we present a case of IPA in a renal transplant recipient who was efficaciously cured with aerosolized amphotericin B lipid complex (aABLC) after developing voriconazole hepatotoxicity.

CASE REPORT

The 67-years-old woman underwent kidney transplant in 2011 because of hepatorenal polycystic disease. The post-transplant period was complicated by the reactivation of CMV infection and severe chronic renal failure (Chronic Kidney Disease stage 5). Her immunosuppression was maintained using tacrolimus and prednisone. In November 2012 the patient presented sudden nightly hemoptysis. The exams led to a diagnosis of IPA “proven” according to EORTC/MSG classification: presence of risk factors (organ transplant, prolonged therapy with steroids and calcineurin inhibitors); hystopathologic exam of the lung tissue displaying acute and chronic flogistic infiltrate with aspects of organizing pneumonia, fragments of fibrous tissue representing abscessual wall, PAS-positive fungal hyphae; high-resolution computer tomography (HRCT) showing wide parenchimal consolidation with open bronchi and superior right lobe cavitation. The immunosuppression was therefore reduced to only prednisone and an oral therapy was started with voriconazole 200 mg q12 h. At the same time the patient took intravenous ABLC (5 mg/kg/day) which was suspended after 7 days because of the worsening of the renal function (haemodialysis became necessary). During this treatment the HRCT was repeated which showed a consolidation with open bronchi on the side segment of the medium lobe and an opacity in resolution in the lower left lobe. The positron emission tomography CT (PET-CT) scan showed two flogistic con-
solidations in the right superior lobe and lower left lobe (respectively SUV 3.6 and diameter 3 cm, SUV 5.6 and diameter 5.5 cm). Galactomannan antigen determination on bronchoaspirate resulted positive (index 0.8). Serum Beta-D-Glucan resulted in sequence >523 pg/ml, 400 pg/ml, 270 pg/ml, 368 pg/ml. The therapy with voriconazole was suspended after 50 days because of an important rise of transaminases and gamma-glutamyl transferase (GGT). A monotherapy was therefore started with aerosolized amphotericin B lipid complex (aeABLC) 50 mg/day using a Medeljet PRO (Medel®) nebulizer. The follow-up was repeated on average every 3 months from January to December 2013. The HRCT after 3 months showed a partial cleansing of the previously described consolidation of the medium lobe and complete cleansing of that localized in the lower left lobe. The following HRCTs resulted superimposable. The PET-TC after 9 months didn’t show areas of increased metabolism but only a metabolically inactive stria in the right lung. Serum Beta-D-Glucan reduced progressively until it became negative after 11 months (in sequence 278 pg/ml, 251 pg/ml, negative). Despite the immunosuppression (metilprednisolone 8 mg/day) the patient did not show any sign of the disease or adverse effects to request the suspension of the aerosolized treatment in the following 12 months. The number of weekly nebulizations was gradually reduced and then suspended after 13 months.

**DISCUSSION**

The incidence of invasive aspergillosis 12 months after transplantation varies according to the transplanted organ with major frequency in lung transplant (2.4-13%) [4]. Mortality is still high despite therapies with demonstrated in vitro activity, due principally to the limited penetration of the antifungal drugs in the infected tissue or delay in the diagnosis.

Among SOTs, renal transplant has a minor incidence of IPA (0.7-4%), while mortality reaches 80%. Risk factors, i.e. the use of immunosuppressants (especially steroids) and the failure of the transplant resorting in haemodialysis, also complicate the treatment since they induce pharmacological interactions, drug-related nephrotoxicity and hepatotoxicity [5]. In particular D-AMB is known for its infusion-related adverse effects and nephrotoxicity, substantially reduced with the use of the lipid formulations. The hepatotoxicity is more frequent with voriconazole than other antifungals including AMB (risk of liver enzymes elevation and treatment discontinuation of 11.6% and 0-2.6% respectively) [6]. Voriconazole interacts with a lot of drugs such as ciclosporin and tacrolimus and can cause hepatitis, cholestasis and fulminant hepatic failure; in the case of CICr being <50 mL/min intravenous delivery of voriconazole is not recommended because the carrier of the intravenous formulation, sulfobutyl ether B-cyclodextrin, accumulates in patients with impaired renal function. On the other hand oral delivery leads to subtherapeutic levels in 20% of cases [7].

In our case report intravenous ABLC was suspended after a few days because of a deterioration of renal function. Voriconazole was interrupted after 50 days because of a significant rise in the liver enzymes. The choice of continuing the treatment with aeABLC was based on the following scientific evidences:

- During pneumonia the aerosol delivery system obtains excellent local concentrations of the drug in connection with a reduced passage into the circulation and limited systemic effects. Studies on animals and lung transplant recipients have demonstrated a higher lung penetration and longer half-life of aeABLC compared to aeD-AMB in broncho-alveolar lavage (BAL) [8]. The recommended dosage of lipid formulation is 25-50 mg/day, double in intubated subjects. The nebuliser should generate particles 2-5 µm in diameter in order to disperse the drug efficiently [9].

- The main clinical studies on aeAMB concern prophylaxis of subjects at high risk. Borro et al., in a retrospective multicentre study, analysed the incidence of invasive fungal infections (IFI) 3 months after lung transplantation in 60 patients undergoing a prophylaxis with aeABLC: only one patient (1.7%) developed a possible IFI by *Aspergillus fumigatus* [10]. Rijnders et al. described a reduction of 70% in the incidence of IFI in a population of subjects affected by haematological malignancies and neutropenia undergoing prophylaxis with aeAMB compared to patients without prophylaxis [11]. There are few studies about treatment of IFI with lipid formulation of aeAMB, mainly associated to systemic antifungals. Safdar et al., in
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A recent retrospective study involving 32 immunocompromised adults with IFI, observed a good tolerance to the therapy and resolution of the disease in 50% of the subjects [12]. A single case is described of invasive lung infection caused by *Rhizomucor* e *Pseudallescheria boydii* in a 61-years-old man undergoing HSCT complicated by graft-versus-host-disease, treated with aeABLC 50 mg/day for 3 weeks with complete recovery [13].

Several studies have demonstrated low or undetectable serum concentrations of AMB following aerosolized administration. The lipophilic nature of AMB has aroused worries about a possible detrimental impact on pulmonary surfactant, but studies concluded that surfactant alteration is due to the deoxycholate portion and not to the drug molecule [14]. Serum creatinine levels was monitored during administration of aeAMB without significant increase [15]. The effects of this therapy on the respiratory system is not clear: a decline in respiratory function was found with variable frequency (from 0 to 40%) and it was not associated with symptoms or treatment discontinuation. Modest symptoms such as cough or wheezing were common, however most of the studies included lung transplant recipients or subjects with other pre-existing respiratory diseases, making these data controversial [14]. Palmer et al. evaluated the effects of the aerosolized liposomes on transbronchial biopsy samples, observing no evidence of tissue toxicity, lipoid pneumonia or acute rejection due to aeAMB [16]. Nausea and taste perversion are less frequent after inhalation of aeABLC, which seems to nebulize more completely than D-AMB leading to less oral deposition and fewer associated gastrointestinal side effects [10].

**CONCLUSION**

Invasive aspergillosis can occur late after transplantation in patients with persistent risk factors (chronic rejection, renal impairment, CMV infection etc). We report the first described case of invasive pulmonary aspergillosis cured with aerosolized amphotericin B lipid complex after two first-line therapies with L-AMB and voriconazole were suspended because of toxicity. Although further studies are required to define the efficacy of this treatment, it appears to be a promising resource able to achieve excellent pulmonary concentrations with low risk of systemic toxicity. This highlights the importance of alternative therapies useful in patients with difficult-to-treat fungal lung disease.

**Keywords:** Invasive pulmonary aspergillosis, aerosolized amphotericin b lipid complex, renal transplant.

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**SUMMARY**

Invasive pulmonary aspergillosis (IPA) is an emerging life-threatening infection in immuno-compromised patients. The incidence of IPA following kidney transplantation is low (between 0.7 and 4%), yet mortality remains unacceptably high (75-80%). A first line therapy with voriconazole or lipid formulations of amphotericin B is often limited by co-morbidities, adverse effects and drug interactions. The case within this publication is the first described report of IPA in a renal transplant recipient responding to aerosolized amphotericin B lipid complex.

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**RIASSUNTO**

L’aspergillosi polmonare invasiva è causa emergente di morbosità e mortalità nell’immunodepresso. Dopo trapianto renale l’incidenza è bassa (0,7-4%) ma la mortalità estremamente elevata (75-80%). Spesso l’utilizzo dei farmaci di prima scelta (voriconazolo e amfotericina B formulazione lipidica) è limitato da comorbidità, effetti collaterali e interazioni farmacologiche. Riportiamo il primo caso descritto in letteratura di aspergillosi invasiva in paziente nefrotrapiantata guarita dopo terapia di salvataggio con amfotericina B complessi lipidici aerosolizzata.
REFERENCES


