

Successful treatment of subcutaneously disseminated aspergillosis with caspofungin acetate in an allogeneic peripheral blood stem cell transplantation patient

We present a patient with acute myeloid leukaemia who developed subcutaneously disseminated aspergillosis after allogeneic peripheral stem cell transplantation (PSCT). Disseminated aspergillosis after stem cell transplantation has a high mortality despite treatment with amphotericin B or one of the azoles. Aspergillosis in our patient was refractory to amphotericin B and itraconazole but was successfully treated with caspofungin acetate.

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Introduction

Disseminated aspergillosis refers to an opportunistic infection by *Aspergillus* species involving more than one non-contiguous site. In 60% of cases disseminated aspergillosis follows invasive pulmonary aspergillosis. The incidence of pulmonary invasive aspergillosis after allogeneic PSCT has been reported as 4-10%^{1,2}. After transplantation, mortality from disseminated aspergillosis remains high (88.1%-90%) despite treatment with amphotericin B and/or itraconazole^{2,3}. Cutaneous aspergillosis occurs primary at sites of skin injury or secondary to disseminated aspergillosis. Subcutaneous disseminated aspergillosis in an immunocompromised patient was only recently described⁴. This patient was treated with amphotericin B but finally died. Here, we present the second patient with disseminated subcutaneous aspergillosis. Her disease was refractory to amphotericin B and itraconazole but was successfully treated with caspofungin acetate.

Case report

A 53-year-old woman was diagnosed with acute myeloid leukaemia (FAB classification M1) in September 1999. After two courses of induction chemotherapy she received an allogeneic PSCT from an HLA identical sibling after total body irradiation and cyclophosphamide. At the end of the pancytopenic period she developed severe desquamative mucositis leading to respiratory failure which required two days of mechanical ventilation. No infections were found. After three weeks she developed graft-versus-host-disease (GVHD) grade 3 for which treatment with high dose prednisone was started. CMV reactivation was treated by ganciclovir. She recovered and was dismissed six weeks after transplantation with GVHD grade 1.

Fourteen weeks after transplantation she reported five painful subcutaneous nodules and severe fatigue and was admitted to the hospital. Medication consisted of prednisone 40 mg daily, mycophenolate mofetil, ganciclovir, fluconazole and co-trimoxazole. Physical examination showed GVHD grade 1 of the skin, subcutaneous nodules on her back, belly and thighs without ulceration of the overlying skin. Body temperature was 36.2°C. Laboratory tests revealed: haemoglobin 9.8 g/dl, WBC $7.0 \times 10^9/l$ with normal differential count, platelets $6 \times 10^9/l$, alkaline phosphatase 105 U/l, gamma GT 346 U/l and bilirubin 12 $\mu\text{mol/l}$. Biopsy specimen of one of the nodules showed fungal hyphae typical of *Aspergillus* species (figure 1 and 2) and culture confirmed *Aspergillus fumigatus*. Computer tomography showed minimal lesions suspected to be infectious in the right upper lobe

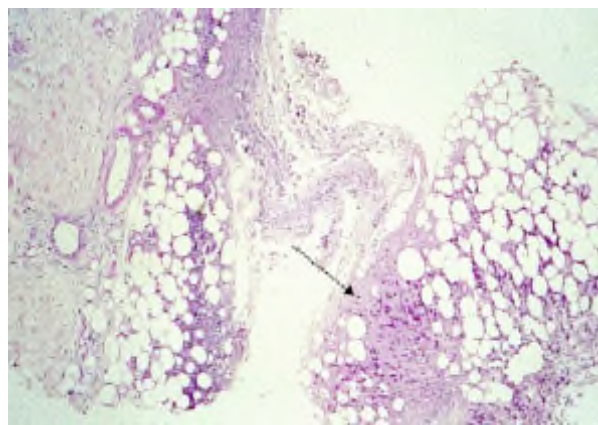


Figure 1. Subcutaneous localisation of hyphae

but no cavitation. Echocardiography was normal. Amphotericin B 1 mg/kg was started and prednisone tapered. After two weeks itraconazole 200 mg p.o. twice daily was added because new lesions appeared. These lesions were progressive and treatment was switched to voriconazole (loading dose 6 mg/kg, daily dose 4 mg/kg i.v.). Her clinical situation deteriorated due to sepsis with *E.Coli* and to progressive GVHD of the skin and liver. After successful treatment with antibiotics and mycophenolate mofetil, she developed pancytopenia. Recurrence of acute leukaemia was ruled out by marrow examination. Short-tandem-repeat analysis revealed 100% donor cells. Persistent pancytopenia due to medication was suspected. After discontinuation of co-trimoxazole without improvement of blood counts, voriconazole was discontinued despite a slight positive effect on the subcutaneous nodules. Caspofungin acetate was started (loading dose 70 mg, daily dose 50 mg i.v.) after which she slowly recovered. The dose was adjusted to 50 mg every other day because of deteriorating liver function without other signs of progressive GVHD (highest bilirubin 228 $\mu\text{mol/L}$). Five weeks after starting caspofungin acetate the subcutaneous nodules had almost disappeared and she was discharged. Caspofungin treatment was continued during five months at a dose of 50 mg three times a week. Twelve months after discontinuation of caspofungin acetate she is in complete remission and in good condition. One of three remaining little nodules was surgically excised and showed no evidence of *Aspergillus fumigatus*.

Discussion

A review spanning 1995 through 1999 reports overall mortality from aspergillosis of 58% and after bone marrow transplantation of 86.7%³. For years the treatment of choice has been amphotericin B. Because of intolerable side effects (nephrotoxicity, infusion-related fever and chills), second line drugs like lipid formulations of amphotericin B, itraconazole and voriconazole have been introduced. A trend towards lower mortality after use of lipid amphotericin B and itraconazole was reported³, but no randomised studies have confirmed this. Recently, lower mortality after treatment of invasive aspergillosis with voriconazole was demonstrated in a randomised study⁵. New therapeutic options have been investigated due to intolerability of amphotericin B, the price of the lipid formulation and the increasing (acquired or intrinsic) resistance for azoles. The (1,3)-

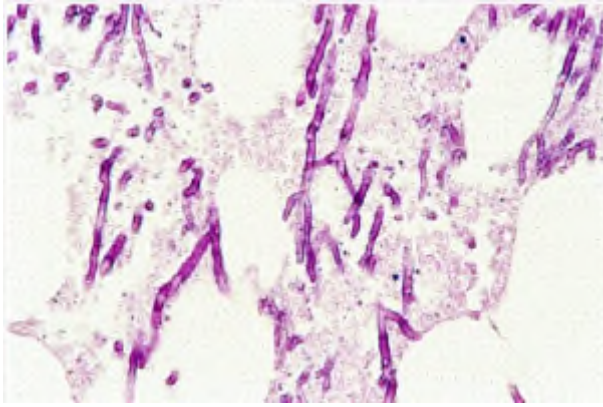


Figure 2. Septated hyphae with angle branching

D-glucan synthase inhibitors, now designated echinocandins, disrupt cell wall glucan formation through non-competitive inhibition of the enzyme complex (1,3)-D-glucan synthase. This mechanism of action is different from that of amphotericin B and azoles. (1,3)-D-glucan synthase is absent from mammalian cells⁶. The spectrum of activity of echinocandins includes *Aspergillus* and *Candida* species. Caspofungin acetate was found to be superior to amphotericin B in treating candidal esophagitis (response rates 89% vs. 63%). Furthermore, 56 immunocompromised patients with sino-pulmonary or disseminated aspergillosis who were refractory (82%) or intolerant (18%) to amphotericin B, its lipid formulations or azoles were treated with caspofungin acetate and a favourable response was reported in 41% of cases⁸. For disseminated aspergillosis the response rate was 20%. Caspofungin acetate was generally well tolerated. Adverse effects included elevation of serum transaminases (in 10.8%), decreased serum potassium (10.8%) and increased creatinin levels (1.5%). The drug is cleared by the liver necessitating dosage adjustments for patients with hepatic insufficiency. No pharmacokinetic interaction with amphotericin B, itraconazole or mycophenolate was observed. Recently, successful combination therapy of caspofungin acetate and itraconazole in two patients with invasive aspergillosis was reported⁹. Cyclosporine A elevates caspofungin acetate levels and their concomitant use is not recommended. We describe the second patient with proven disseminated subcutaneous aspergillosis. The first

patient died, but our patient, who's disease was refractory to amphotericin B and itraconazole, was successfully treated with caspofungin acetate and 20 months after transplantation she has no signs of *Aspergillus* infection. Caspofungin acetate seems to be a promising drug for patients with disseminated aspergillosis.

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References

1. Martino R, Subira M, Rovira M, Solano C, Vazquez L, Sanz GF et al. Invasive fungal infections after allogeneic peripheral blood stem cell transplantation: incidence and risk factors in 395 patients. *Br J Haematol* 2002; 116(2):475-482.
2. Jantunen E, Ruutu P, Piilonen A, Volin L, Parkkali T, Ruutu T. Treatment and outcome of invasive *Aspergillus* infections in allogeneic BMT recipients. *Bone Marrow Transplant* 2000; 26(7):759-762.
3. Lin SJ, Schranz J, Teutsch SM. Aspergillosis case-fatality rate: systematic review of the literature. *Clin Infect Dis* 2001; 32(3):358-366.
4. Cornely OA, Pels H, Bethe U, Seibold M, Toepelt K, Soehngen D et al. A novel type of metastatically spreading subcutaneous aspergillosis without epidermal lesions following allogeneic stem cell transplantation. *Bone Marrow Transplant* 2001; 28(9):899-901.
5. Herbrecht R, Denning DW, Patterson TF, Bennett JE, Greene RE, Oestmann JW et al. Voriconazole versus amphotericin B for primary therapy of invasive aspergillosis. *N Engl J Med* 2002; 347(6):408-415.
6. Hoang A. Caspofungin acetate: an antifungal agent. *Am J Health Syst Pharm* 2001; 58(13):1206-1214.
7. Villanueva A, Gotuzzo E, Arathoon EG, Noriega LM, Kartsonis NA, Lupinacci RJ et al. A randomized double-blind study of caspofungin versus fluconazole for the treatment of esophageal candidiasis. *Am J Med* 2002; 113(4):294-299.
8. Maertens J, Raad L, Sable SA, Ngai A, Berman R, Patterson TF et al. Multicenter, noncomparative study to evaluate safety and efficacy of caspofungin acetate in adults with invasive aspergillosis refractory or intolerant to amphotericin B, amphotericin B lipid formulations, or azoles. Paper presented at 40th Interscience Conference on Antimicrobial Agents and Chemotherapy, Toronto, Ontario, abstract 1103. 17-9-2000.
9. Rubin MA, Carroll KC, Cahill BC. Caspofungin in combination with itraconazole for the treatment of invasive aspergillosis in humans. *Clin Infect Dis* 2002; 34(8):1160-1161.