Case Report

Successful treatment of Candida krusei fungemia with amphotericin B and caspofungin

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We report a leukemic patient with C. krusei fungemia who failed to respond to liposomal amphotericin B therapy alone. The addition of caspofungin eradicated infection and was well tolerated. Our report is the first to describe successful treatment of a patient with invasive C. krusei infection using this combination of antifungals. Combination therapy could be a useful treatment option for invasive candidosis, particularly when caused by more resistant species such as C. krusei.

Keywords Candida krusei, fungal infections, antifungal therapy, leukemia

Introduction

Candida krusei is an uncommon isolate in blood cultures, representing 2.9% of candidemias in a survey of hospitals in England and Wales [1]. However all the C. krusei in this survey were from haematology patients (25% of candidemias in this group). It has intrinsic resistance to fluconazole and high levels of resistance to flucytosine. We describe the successful treatment of a leukemic patient with C. krusei fungemia using amphotericin B and caspofungin in combination, after he failed to respond to amphotericin B alone.

Case report

A 24-year-old man was admitted with neutropenia (<0.1 x 10⁹/l) following chemotherapy for relapsed acute lymphoblastic leukemia. He was febrile and had been vomiting. His medication included prophylactic fluconazole 50 mg once daily. Blood cultures taken peripherally and through the Hickman line yielded C. krusei, identified on the Vitek 1 system (bioMerieux, Basingstoke, UK). He was commenced on intravenous liposomal amphotericin B (Ambisome, Gilead) 1 mg/kg. This was increased to 3 mg/kg the following day and the Hickman line was removed. Culture of the tip did not show any growth. With persisting neutropenic fever the dose was then increased to 5 mg/kg and he was given granulocyte colony stimulating factor (G-CSF). He developed a widespread maculopapular rash, thought at first to be allergic. A transthoracic echocardiogram did not show any vegetations and CT abdomen did not show any lesions in the liver, spleen or kidneys. Blood cultures were repeated on the fourth day of amphotericin B after his temperature reached 40.3°C and again yielded C. krusei. At this point intravenous caspofungin was added (70 mg loading dose followed by 50 mg once daily). Despite this and his neutrophil count rising to 2.6 x 10⁹/l, he remained pyrexial. Blood cultures taken three days after starting caspofungin still yielded C. krusei. Due to the continuing fungemia, and with his neutrophil count having further risen to 3.3 x 10⁹/l, a deep source of infection was suspected. However, a transesophageal echocardiogram was normal and fundoscopy did not reveal any sign of endophthalmitis. Over the next few days his temperature and rash (thought now to have been due to disseminated candidosis) slowly resolved. Blood cultures taken 12 days after admission yielded a coagulase-negative staphylococcus and he was commenced on intravenous teicoplanin. However no yeast was recovered from this
culture. He continued to improve and further blood cultures were negative. He completed a total of 21 days of intravenous amphotericin B (Ambisome) and caspofungin, 17 days of which were after the last positive blood culture for *C. krusei*. He was subsequently treated with oral voriconazole 200 mg twice daily for four weeks. He remains well and has now had bone marrow transplantation.

The *C. krusei* isolate was sent to the Specialist Mycology Laboratory in Glasgow for sensitivity testing. This was performed using broth dilution based on current CLSI (formerly NCCLS) guidelines [2] and also the YeastOne® broth microdilution plate (Trek Diagnostic Systems Ltd, East Grinstead, UK). The MIC to amphotericin B was 1 mg/l, fluycytosine 16 mg/l, voriconazole 0.125 mg/l and caspofungin 0.25 mg/l.

**Discussion**

This patient developed *C. krusei* infection after receiving fluconazole prophylaxis, a recognized risk factor [3]. Amphotericin B and fluycytosine are often used in combination because of synergy in the treatment of candidemia [4]. However in a study of 184 clinical *C. krusei* isolates only 5% were sensitive to fluycytosine, as defined by an MIC of 4 mg/l or less [5]. Concern about this (prior to sensitivity results being available) led us to add caspofungin to amphotericin B. This new antifungal is one of the echinocandins, licensed for the empirical treatment of febrile neutropenia and invasive fungal infections. It inhibits β-glucan synthesis in the fungal cell wall, a different mechanism to other antifungals in clinical use, showing good activity against a wide range of *Candida* spp., including *C. krusei* [6]. A randomized controlled trial has shown caspofungin to be as effective as amphotericin B in the treatment of invasive candidiasis [7]. We added caspofungin to amphotericin B therapy because after four days of amphotericin B the patient was still unwell and blood cultures showed ongoing fungemia. Although candidaemia is known to resolve relatively slowly with treatment, time-kill-curve experiments have shown that the time to reach the fungicidal endpoint is much longer for *C. krusei* (>40 h) compared to *C. albicans* (2 h) [8]. This may partly explain the lack of fungal eradication using amphotericin B alone despite an MIC of 1 mg/l.

Caspofungin and amphotericin B have been used in combination for a variety of fungal infections where initial monotherapy (usually with amphotericin B) was unsuccessful. Infections including aspergillosis and invasive candidiasis (*C. albicans*, *C. glabrata*, *C. tropicalis*) have responded well [9]. However it is important to consider whether the switch to caspofungin or its addition is the best therapeutic option. There are reports of disseminated candidiasis which did not respond to amphotericin B but were then successfully treated with caspofungin alone [10,11]. *In vitro* data has shown amphotericin B and caspofungin to have an additive effect [12]. However in the same study, using the disseminated candidiasis mouse model (azole-resistant *C. albicans*), this combination of antifungals produced a synergistic reduction in candidal burden in the kidney and the brain. Mouse survival was prolonged when compared with amphotericin B alone, although this difference was not significant. Another study using the disseminated candidiasis mouse model (*C. albicans*) also showed synergistic activity for these two agents [13]. This data suggests that combination therapy may be useful in some clinical situations. The underlying mechanisms of additive or synergistic effects are not known. However, it is likely that cell wall damage from the action of caspofungin allows amphotericin B easier access to fungal cell membrane, where it binds to ergosterol and leads to cell lysis. A further reason why combination therapy may have a role is that resistance to caspofungin has emerged during treatment of a *C. krusei* infection [14]. A patient developed disseminated *C. krusei* infection in the lungs and brain after 12 days of caspofungin monotherapy. Combination therapy may make such emergence of resistance less likely.

Our report describes the successful treatment of a patient with invasive candidosis using amphotericin B and caspofungin. Combination therapy could be a useful treatment option for these infections, particularly those caused by more resistant species such as *C. krusei*.

**References**