Spondylodiscitis Caused by Candida krusei: Case Report and Susceptibility Patterns

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A 62-year-old man with amphotericin B-resistant Candida krusei spondylodiscitis, following an episode of candidemia caused by the same strain, was successfully treated with caspofungin plus voriconazole. Amphotericin B fungicidal concentrations were better predictors of the clinical outcome than were MICs. This is the first case of C. krusei spondylodiscitis reported in the literature.

CASE REPORT

A 62-year-old man was diagnosed with acute myeloid leukemia (FAB-M2) in May 2002. The treatment consisted of idarubicin plus citarabine (3 + 7 regimen), achieving complete remission. In July 2002, consolidation was given without problems. Three months later, intensification chemotherapy (mitoxantrone plus citarabine) was administered. Oral fluconazole (100 mg daily) was given for antifungal prophylaxis. On day 10 after chemotherapy, during the severe neutropenia period, the patient presented with fever, myalgia, and disseminated painful skin nodules. Several blood cultures were positive for C. krusei, but culture of a specimen obtained by fine-needle aspiration of the skin lesion was negative. At that moment, the cumulative dose of fluconazole was 1,500 mg. Antifungal therapy was started with liposomal amphotericin B (3 mg/kg/day) for 2 weeks in association with standard-dose caspofungin for 4 weeks. Other therapeutic measures included removal of the central venous catheter (the tip culture was negative) and administration of filgrastim until neutropenia recovery. In addition, he received oral itraconazole (200 mg twice a day for 4 weeks) as an outpatient. In January 2003, 4 months after the candidemia episode, he presented with fever and severe dorsal back pain. Physical examination did not reveal any neurological deficit. A computed tomography (CT) scan showed a left paravertebral mass, with soft tissue involvement at the D5-D6 level. The magnetic resonance imaging (MRI) findings were consistent with spondylodiscitis (Fig. 1), and the culture of a specimen collected by CT-guided fine-needle biopsy yielded C. krusei. Because of the presence of high (≥ 8 mg/liter) amphotericin B minimum fungicidal concentrations (MFCs), a combination of standard doses of caspofungin and voriconazole was administered for 6 weeks, with a favorable clinical response. Posterior voriconazole maintenance therapy was given, and surgical treatment was not required. After a 6-month follow-up, the evolution remained good on the basis of clinical and MRI evidence, but the patient died 2 months later due to a relapse of leukemia.

The two C. krusei strains isolated from blood (CK-18) and biopsy (CK-19) specimens were identified by molecular techniques, according to the method of Esteve-Zarzoso et al. (9). Strain characterization was performed by PCR amplification and subsequent restriction analysis of the 5.8S-ITS region. To confirm the correct identification, an amplification of partial 26S rRNA gene sequences was carried out. The results obtained were compared with the database available online at the IATA website (http://motor.edinfo.es/iata/), and the two strains were identified as Issatchenkia orientalis (a teleomorph of C. krusei).

Susceptibility to amphotericin B (100% growth inhibition) was determined according to the M27-A2 document, using Sensititre YeastOne (Trek Diagnostic Systems) and Etest (AB biodisk, Sweden) methods, and by time-killing curves (3). The MICs of caspofungin and itraconazole were determined by the M27-A2 method, and those of voriconazole were determined by the M27-A2 and Etest methods. The MFC of amphotericin B was determined by subculturing the entire volume of each clear MIC well (0.2 ml) on two Sabouraud dextrose agar plates (5). The interaction of caspofungin with either amphotericin B or voriconazole determined by Etest and checkerboard methods (4) was calculated on the basis of fractional inhibitory concentration index.

Invasive fungal infections caused by Candida species have increased significantly over the past two decades. In high-risk areas such as hematology units, candidemia rates are six episodes per 1,000 admissions (1). Fluconazole prophylaxis has been associated with a decrease in susceptible species (C. tropicalis and C. albicans) and has been the most important determinant of the relative increase of C. krusei and C. glabrata. This trend is more evident in patients with hematological malignan-
cies than in those with solid tumors (16). Deep infections by C. krusei have been frequently noted in severely ill patients previously exposed to azole agents. This species is claimed to be intrinsically resistant to fluconazole and may have reduced susceptibility to amphotericin B.

Candida osteomyelitis is a recognized late complication of fungemia, occurring several months after the initial episode (2, 6–8, 10, 13). On the other hand, Candida vertebral osteomyelitis remains a rare condition (11, 14, 15). The species more frequently involved are C. albicans (62%), C. tropicalis (19%), and C. glabrata (14%). No case of Candida spondylodiscitis with C. krusei has been reported to date. Furthermore, a MEDLINE literature search revealed only one case of bone infection with this organism: a C. krusei sternal osteomyelitis after sternotomy for coronary bypass grafting (12).

There is no relationship between the duration of treatment and the occurrence of late complications. In a Candida spondylodiscitis series, candidemia was documented in 65% of the cases. Severe neurological complications may occur depending on the site of infection. Imaging techniques (CT and MRI) are useful for a topographic diagnosis and outcome control. However, etiologic diagnosis requires biopsy. In the present case, molecular identification of isolates from blood and fine-needle-biopsy specimens by analysis of the region 5.8S-ITS confirmed that both were the same strain. It should be kept in mind that C. krusei is a pathogen with decreased susceptibility not only to fluconazole (all isolates should be considered resistant) but also to amphotericin B. It is important that this resistance pattern does not extend to the newer triazoles or the echinocandins, which have excellent activity against C. krusei. In the present case, according to the MICs, both C. krusei isolates were susceptible to amphotericin B, voriconazole, and caspofungin as determined by the three methods (MICs: amphotericin B, ≤1 mg/liter; voriconazole, ≤1 mg/liter; itraconazole, 0.25 mg/liter; and caspofungin, ≤0.25 mg/liter). However, high amphotericin B MFC values (16 mg/liter) were consistent with clinical resistance to amphotericin B. No interactions were found between amphotericin B plus caspofungin and voriconazole plus caspofungin, as determined by both checkerboard (fractional inhibitory concentration indices of >0.5 and <1.5) and Etest methods (the MIC of the combination was that of the most active drug). As determined by time-kill studies, a 95% reduction in viable cells was obtained with 2 mg of amphotericin B/liter and 8 mg of caspofungin/liter after 24 h of incubation.

Based on these in vitro results, although evidence from clinical trials is lacking, combination antifungal therapy seems to be a logical approach to treating severe deep-seated fungal infections. In our patient, the clinical course was favorable and vertebral surgery was unnecessary. This is the first report of spondylodiscitis caused by C. krusei, and it confirms the pathogenic role of this species in immunosuppressed patients.

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REFERENCES