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Candida krusei fungaemia: antifungal susceptibility and clinical presentation of an uncommon entity during 15 years in a single general hospital

Patricia Muñoz*, Mar Sánchez-Somolinos, Luis Alcalá, Marta Rodríguez-Créixems, Teresa Peláez and Emilio Bouza

Clinical Microbiology and Infectious Diseases Department, Hospital General Universitario 'Gregorio Marañón', Doctor Esquerdo 47, 28006 Madrid, Spain

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***Background*: *Candida krusei* fungaemia is an uncommon entity described in immunocompromised patients previously exposed to azole agents.**

***Methods*: From 1988 to 2003, 13 episodes of *C. krusei* fungaemia (2.3% of all fungaemias) were detected in our institution and compared with 39 *Candida albicans* controls. Susceptibility testing was carried out with the modified microdilution method according to NCCLS recommendations.**

***Results*: Underlying conditions were: HIV infection (4), haematological malignancies (4), organ transplantation (2), abdominal surgery (2) and lactose intolerance (1). Nine patients (69%) were not neutropenic. In comparison with *C. albicans*, patients with *C. krusei* infection had more commonly received antifungal agents (54% versus 15%, $P = 0.006$), had a haematological disease (31% versus 3%, $P = 0.03$), or a transplant (15% versus 3%, $P = 0.08$), were on corticosteroids (47% versus 13%, $P = 0.01$) and were neutropenic (31% versus 0%, $P < 0.001$). Patients with *C. albicans* had more surgical interventions (41% versus 15%, $P = 0.09$) and bladder catheters (61% versus 31%, $P = 0.05$). The most common origin for *C. albicans* was a catheter (41% versus 0%; $P = 0.006$) whereas for *C. krusei* the most common origin was unknown (69% versus 20%; $P = 0.001$). *C. krusei* presented more commonly with skin lesions in neutropenic patients (23% versus 5%; $P = 0.05$). Multivariate analysis of these differential characteristics showed that the only factor that independently predicted the presence of *C. krusei* fungaemia was the administration of antifungal agents before the fungaemia (RR: 6.4; $P = 0.009$; 95%CI 1.6–25.99). Overall mortality of *C. krusei* fungaemia was 38% (*C. albicans* 49%). Except for voriconazole (MIC_{90} 0.125 mg/L), azoles and 5-flucytosine had poor activity against *C. krusei*, whereas amphotericin (MIC_{90} 1 mg/L) and LY-303366 (MIC_{90} 0.06 mg/L) showed good activity.**

***Conclusion*: *C. krusei* fungaemia incidence remains low despite widespread use of azoles. It may occur outside the setting of cancer patients with previous antifungal use. The presence of skin lesions should be a warning sign.**

Keywords: candidosis, candidaemia, transplantation, HIV, neutropenia

Introduction

Nosocomial infections caused by *Candida* spp. have significantly increased during the last two decades[1] and remain an important cause of morbidity and mortality in critically ill and immunocompromised patients.[2,3]

In recent years, a sharp increase in the incidence of infections caused by non-*albicans Candida* (NAC) species has been reported.[4] *C. krusei* has been described in severely ill patients previously exposed to azole agents. It is claimed to be intrinsically resistant to fluconazole and may have reduced susceptibility to amphotericin B. Few series have specifically

*Corresponding author. Tel: +34-91-58684-53; Fax: +34-91-5044906; E-mail: pmunoz@micro.hggm.es

addressed the epidemiological and clinical characteristics of *C. krusei* and most included only patients with cancer[5–7] or bone marrow transplantation (BMT).[8] We compared all our *C. krusei* patients with *C. albicans* fungaemia patients (controls) in order to identify the risk factors and clinical characteristics of *C. krusei* fungaemia. We randomly selected three controls for each case only matched by year of occurrence.

The antifungal susceptibility pattern of *C. krusei* is also provided.

Materials and methods

Study design

Between 1988 and 2003, 569 episodes of significant fungaemias were detected in our 1750 bed institution, and 13 cases corresponded to *C. krusei* (2.3%). These isolates of *Candida krusei* recovered from blood cultures (stored at −70°C) in our microbiology laboratory were included in the study.

Clinical reports of the patients with an isolate of *C. krusei* were reviewed according to a pre-established protocol and each one was compared with three cases of *C. albicans* fungaemia. The controls were only matched with respect to year of positive blood culture and selected by means of a random number table.

A patient was considered to have significant candidaemia if *C. krusei* or *C. albicans* was isolated from at least one blood culture specimen associated with fever or signs of infection. Source of fungaemia was defined as a culture-positive site or a clinically evident site of infection. Neutropenia was defined as an absolute neutrophil count <500 cells/mm^3. Complications of fungaemia were defined as endocarditis, endophthalmitis, skin infiltrates etc. following fungaemia. Related mortality was defined as death occurring within 5 days of the fungaemia with concurrent signs of active infection and no other apparent cause.

From 1988 to October 1995, blood samples were processed by using the automated system BACTEC-NR (Becton Dickinson, MD, USA) and thereafter, with the BACTER-9240 instrument (Becton Dickinson). In the first period, all vials were incubated at 35°C for 7 days, while in the second period vials were shaken continuously for 5 days.

Statistical methods

Categorical data were analysed using a χ^2 or Fisher exact test (two-tailed), and the unpaired Student's *t*-test was used for continuous variables. Stepwise logistic multivariate analysis to identify differential characteristics of *C. krusei* fungaemia was carried out. Variables with a *P* value <0.1 in the univariate analysis were included in the multivariate model. All comparisons were considered statistically significant for *P* values of 0.05 or less. Statistical analysis was carried out using the SPSS software system.

Susceptibility analysis

Isolates were thawed and subcultured onto CHROMagar *Candida* plates (Tec-Laim, Madrid, Spain) for 5 days at 35°C to identify possible mixed infections and to assure purity. Identification was confirmed by the Vitek and API ID 32 C (bioMérieux, St. Louis, MO, USA) systems as recommended by the manufacturer. The following antifungals were included in the study: amphotericin B, 5-flucytosine, ketoconazole, fluconazole, itraconazole, voriconazole and LY-303366. The susceptibility study was carried out using a modified microdilution method according to NCCLS recommendations (document M-27A),[9] using antibiotic medium 3 for amphotericin B and RPMI-2% glucose medium for the remaining antifungals.[10,11] The micropanels were incubated for 24–48 h at 35°C. Endpoint readings were defined visually as a full (amphotericin B) or prominent inhibition of growth (for the remaining antifungals). The interpretive breakpoints defined by NCCLS for antifungals are as follows: 5-flucytosine (susceptible, <8 mg/L; intermediate, 8–16 mg/L; and resistant, >16 mg/L), fluconazole (susceptible, <16 mg/L; susceptible dependent upon dose, 16–32 mg/L; and resistant, >32 mg/L) and itraconazole (susceptible, <0.25 mg/L; susceptible dependent upon dose, 0.25–0.5 mg/L; and resistant, >0.5 mg/L). For the remaining antifungals, the following interpretative breakpoints were used: amphotericin (susceptible, <4 mg/L; and resistant, >2 mg/L) and ketoconazole (susceptible, <0.25 mg/L; susceptible dependent upon dose, 0.25–0.5 mg/L; and resistant, >0.5 mg/L). No breakpoints were used for voriconazole and LY-303366.

Results

Between 1988 and 2003, 569 episodes of significant fungaemia were detected in our institution (271 corresponded to *C. albicans*, 170 to *C. parapsilosis*, 13 to *C. krusei* (2.3%) and 115 to other species. The annual distribution of *C. krusei* fungaemias was: five cases in 1990, three in 1992, and one each in 1994, 1996, 1997, 2000 and 2001. No epidemiological link was found between the five patients who had *C. krusei* fungaemia in 1990.

Table 1. MICs (mg/L) of antifungals tested for the *C. krusei* fungaemia isolates

	Range	MIC_{50}	MIC_{90}	SDD-I[a] (%)	Resistance[b] (%)
Amphotericin B	0.5–1	1	1	–	0
5-Flucytosine	2–8	4	8	45.5	0
Ketoconazole	0.5–1	0.5	1	54.5	45.5
Fluconazole[c]	16–32	32	32	100	0
Itraconazole	0.25–0.5	0.25	0.5	100	0
Voriconazole	0.125	0.125	0.125	–	–
LY-303366	0.06	0.06	0.06	–	–

[a]Percentage susceptible dependent upon dose (azoles) or intermediate (5-flucytosine) using the interpretive breakpoint criteria of NCCLS: 5-flucytosine 8–16 mg/L; fluconazole, 16–32 mg/L; itraconazole, 0.25–0.5 mg/L. For ketoconazole, the same breakpoint criteria for itraconazole was used.
[b]Percentage resistant using the interpretive breakpoint criteria of NCCLS: 5-flucytosine >16 mg/L; fluconazole, >32 mg/L; itraconazole, >0.5 mg/L. For the remaining antifungals, the following breakpoints were used: amphotericin B (>2 mg/L) and ketoconazole (>0.5 mg/L).
[c]In a clinical sense, isolates of *C. krusei* are considered inherently resistant to fluconazole, irrespective of the MIC.

Table 2. Clinical data for 13 patients with *C. krusei* fungaemia

Year	Age/sex	Underlying condition	Previous antifungals	Risk factors	Presentation	Other cultures	Origin	Catheter withdrawal	Therapy	Evolution
00	50/F	AML	itraconazole	neutropenia, catheter, steroids, BSA, TPN	fever, hepato-splenic, skin, lung	skin	unknown	yes	AMB	cure
90	67/M	AML	nystatin	neutropenia, steroids, BSA, TPN	fever, lung, chorioretinitis, skin	skin, respiratory tract	unknown	–	AMB +5FC	cure
90	61/F	AML	nystatin	neutropenia, catheter, steroids	fever, myositis, skin	muscle	unknown	yes	AMB +5FC	cure
96	64/M	CLL	fluconazole	neutropenia, iv catheter, steroids, BSA	fever, lung, shock	respiratory tract	unknown	–	AMB	death
90	45/F	kidney Tx with chronic rejection, HCV	–	catheter, indwelling bladder catheter, steroids, BSA	fever	urine	urine	–	AMB	death (unrelated)
92	52/M	liver Tx fulminant hepatic failure	nystatin	iv catheter, indwelling bladder catheter, steroids, BSA, TPN, surgery	fever, shock	urine	unknown	yes	AMB	cure
90	1/F	lactose intolerance	–	catheter, BSA	fever	–	unknown	yes	–	cure
92	32/M	HIV, IVDA	–	IVDA	fever	–	IVDA	–	FLU +AMB	cure
90	36/M	HIV, IVDA	–	IVDA	fever		IVDA	–	–	cure
94	33/M	HIV, IVDA	–	IVDA	fever	urine	IVDA	–	AMB	death
97	29/M	HIV, IVDA, psoriasis	fluconazole	iv catheter, BSA	fever, shock	–	unknown	yes	–	death
01	82/M	gastric carcinoma	–	iv catheter, BSA	fever, shock	–	unknown	yes	FLU, AMB	death
92	81/M	urinary fistula	fluconazole	iv catheter, BSA, bladder catheter	fever	urine	urine	–	–	cure

F, female; M, male; AML, acute myelogenous leukaemia; BSA, broad spectrum antimicrobials; TPN, parenteral nutrition; AMB, amphotericin B; 5FC, 5-flucytosine; CLL, chronic lymphocytic leukaemia; Tx, transplantation; IVDA, intravenous drug abuse.

Susceptibility testing was carried out on the 13 *C. krusei* strains. The MICs are shown in Table 1. With the exception of voriconazole (MIC_{90} 0.125 mg/L), azoles and 5-flucytosine did not have good activity against *C. krusei* (for fluconazole, all isolates have to be considered resistant irrespective of the MIC). On the other hand, amphotericin (MIC_{90} 1 mg/L) and the antifungal LY-303366 (MIC_{90} 0.06 mg/L) showed good activity (Table 1).

Clinical characteristics of the 13 patients with *C. krusei* fungaemia are shown in Table 2. Nine patients were male and median age was 50 years (8 months–82 years). All patients had significant debilitating conditions: HIV infection (4), haematological malignancies (4), solid organ transplantation (2), abdominal surgery due to gastric cancer and urinary fistula after prostatic surgery (1 each) and lactose intolerance (1). Median number of positive blood cultures was 2.5 (1–6).

Fungaemia was community-acquired in four cases (three intravenous drug abusers and one baby with severe diarrhoea due to lactose intolerance). Regarding clinical presentation, the three patients with acute leukaemia had related skin lesions, three patients had lung infiltrates and one had chorioretinitis (Table 2).

Seven patients had received antifungal drugs (non-absorbable or systemic) before the fungaemia (three nystatin, three fluconazole, and one developed a breakthrough fungaemia while receiving itraconazole). Therapy consisted of amphotericin B (nine patients) and four patients did not receive treatment. Therapy was started a median of 2.3 ± 2.6 days after blood cultures were obtained. Three patients recovered despite not receiving antifungal therapy: a neonate with diarrhoea and lactose intolerance, an HIV patient who developed a transient fungaemia after a self-administration of illegal intravenous (iv) drugs and a patient with a urinary tract infection.

Table 3. Comparison of the epidemiological characteristics of patients with *C. krusei* and *C. albicans* fungaemia

Factor	*C. krusei* ($n=13$)	*C. albicans* ($n=39$)	*P* value
Age (median ± S.D.)	50 ± 23	45 ± 21	0.5
Gender			
male	9 (69%)	29 (75%)	0.7
female	4 (31%)	10 (25%)	
Underlying disease			
haematological disease	4 (31%)	3 (8%)	0.03
AIDS	4 (31%)	11 (28%)	0.8
IVDA	4 (31%)	9 (23%)	0.5
transplantation	2 (15%)	1 (3%)	0.08
Risk factor			
neutropenia	4 (31%)	0 (0%)	< 0.001
surgery	2 (15%)	16 (41%)	0.09
parenteral nutrition	3 (23%)	17 (44%)	0.1
iv lines	10 (77%)	34 (87%)	0.3
bladder catheters	4 (31%)	24 (61%)	0.05
previous antimicrobials	9 (70%)	28 (72%)	0.8
previous antifungals	7 (54%)	6 (15%)	0.006
previous azole agents	4 (31%)	4 (10%)	0.07
corticosteroids	6 (47%)	5 (13%)	0.01

Overall mortality was 38.5%, but one out of five deaths was unrelated to the fungaemia (related mortality 30.7%) (Table 1).

For the identification of differential characteristics of *C. krusei* fungaemia, we compared each *C. krusei* patient with three randomly selected *C. albicans* patients (controls). The differences found in the univariate analysis are shown in Table 3. Patients with *C. krusei* had more commonly received antifungal agents before the fungaemia (54% versus 15%, $P=0.006$), had an underlying haematological disease (31% versus 3%, $P=0.03$), or a transplant (15% versus 3%, $P=0.08$), were on corticosteroids (47% versus 13%, $P=0.01$) and were neutropenic (31% versus 0%, $P<0.001$). Patients with *C. albicans* had more frequently undergone a surgical intervention (41% versus 15%, $P=0.09$) and had indwelling bladder catheters (61% versus 31%, $P=0.05$).

With regard to portal of entry, vascular catheters were the most common portal for *C. albicans* (41% versus 0%; $P=0.006$), whereas an unknown origin was the most common portal for *C. krusei* (69% versus 20%; $P=0.001$). *C. krusei* presented more frequently than *C. albicans* with skin lesions (23% versus 5%; $P=0.05$). Skin lesions were necrotic disseminated varicelliform papules and were only detected in neutropenic patients (Figure 1). GI-tract colonization data were not available to localize the possible origin of fungaemia.

Multivariate analysis of these differential characteristics, showed that the only factor that independently predicted the presence of *C. krusei* fungaemia was the administration of antifungal agents before the fungaemia (RR: 6.4; $P=0.009$; 95%CI 1.6–25.99).

There were no significant differences regarding therapy and evolution. We could not find significant differences between the overall mortality rate of *C. albicans* and *C. krusei* fungaemias (49% versus 38%; $P=0.5$), nor between their related mortality (36% versus 31%, $P=0.7$). Overall, the presence of skin lesions due to *Candida* fungaemia was a protective factor (no mortality versus 49%, $P=0.03$), whereas indwelling bladder catheter (mortality rate 57% versus 29% $P=0.04$), intravenous catheter (50% versus 12%, $P=0.04$) and septic shock (100% versus 34%; $P=0.001$) were related to a poorer outcome. Patients with previous surgery (61% versus 35%, $P=0.07$) and total parenteral nutrition (60% versus 34%, $P=0.07$) also showed a trend towards higher mortality.

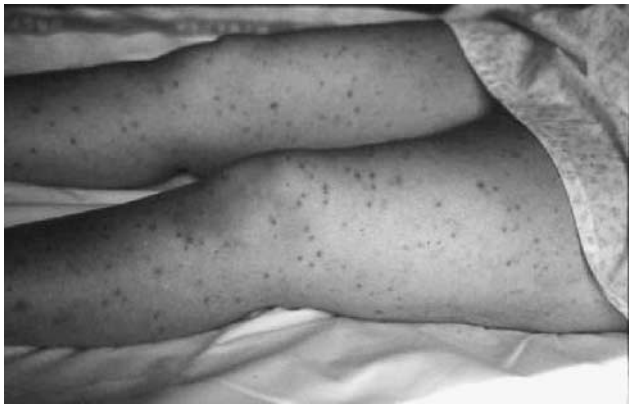

Figure 1. Skin lesions of a patient with *Candida krusei* fungaemia.

Discussion

In our hospital, a general tertiary institution, *C. krusei* represents 2.3% of all episodes of candidaemia, and this proportion has not increased during the last 12 years, despite a widespread use of fluconazole prophylaxis in neutropenic patients and in other areas of the centre (more than 6000 daily defined doses provided in 2001). The estimates of *C. krusei* fungaemia vary between institutions, and also between units in the same institution and over different years. Information comes mainly from units with neutropenic or highly immunocompromised patients, where it may represent from 4% to 61% of all episodes of fungaemia. Wingard *et al.* found that 4% of fungaemia episodes were due to *C. krusei* in patients who had undergone BMT or who had leukaemia.[12] However, in high-risk allogeneic BMT recipients on low-dose fluconazole prophylaxis, or in other neutropenic patients, *C. krusei* accounted for 33.3–61% of the episodes.[8,13] At the M. D. Anderson Cancer Center, 6.8% of all episodes of fungaemia were caused by *C. krusei* and the incidence rose from 5% in 1989–1992 to 10% in 1993–1996.[5]

Most reports of *C. krusei* fungaemia are from cancer centres or units and neutropenia is present in more than 70% of such patients.[5,8] Very few cases have been described in non-cancer patients. In a retrospective 5 year review, Iwen *et al.* identified 203 cases of invasive candidiasis of which eight cases were caused by *C. krusei*. Four of the patients involved had leukaemia, two had breast cancer, one had end-stage liver disease, and one had suffered abdominal trauma.[14] *C. krusei* fungaemia is extremely rare in intensive care units[2] and after solid organ transplantation (SOT). We describe two cases in SOT recipients and have been able to find another three in the literature.[15–17] In our series, we had three episodes in HIV-positive patients and four others have been reported.[18,19] Our episode in a baby with massive diarrhoea and lactose intolerance is exceptional. Fungal overgrowth has been related to diarrhoea, mainly in children,[20,21] and intestinal mucosal lesions may be the origin of the fungaemia.

The clinical condition of our patients probably represents the overall spectrum of *C. krusei* fungaemia in a large institution better than series from cancer centres. When we compared patients with *C. krusei* and *C. albicans* fungaemia, patients with *C. krusei* had more commonly received previous antifungal agents (54% versus 15%, $P = 0.006$), suffered more haematological diseases (31% versus 3%, $P = 0.03$), had received a transplant (15% versus 3%, $P = 0.08$), were on corticosteroids (47% versus 13%, $P = 0.01$) and were neutropenic (31% versus 0%, $P < 0.001$). Patients with *C. albicans* had more frequently undergone a surgical intervention (41% versus 15%, $P = 0.09$) and had indwelling bladder catheters (61% versus 31%, $P = 0.05$).

In our series, *C. krusei* fungaemia was predominantly nosocomial (69%) and was acquired in the community in four cases (three iv drug abusers and one baby with diarrhoea and lactose intolerance). Abbas *et al.* reported that eight (14%) episodes of *C. krusei* fungaemia in cancer patients were considered to be community-acquired.[5] *C. krusei* has been detected on the hands of healthcare workers (potential reservoirs for nosocomial transmission),[22] but there is no evidence of nosocomial dissemination.[23]

It is difficult to argue against the role of prior prophylaxis with azole derivatives (mainly fluconazole) as a predisposing condition for *C. krusei* infection.[12,24] Prophylaxis with fluconazole increases colonization by *C. krusei*.[6,12] The proportion of patients with *C. krusei* fungaemia that had received previous fluconazole ranges from 50% to 90% in different series,[5,13,23,25,26] whereas only 5–10% of patients with *C. albicans* fungaemia had received fluconazole in other studies.[7,23] In our series, seven patients had received antifungals before the fungaemia (3 nystatin, 3 fluconazole, and one developed a breakthrough fungaemia while receiving itraconazole). Nevertheless, in our opinion and that of other authors, the absence of prior fluconazole treatment should not lead physicians to exclude *C. krusei* fungaemia.[8,14,23,27–29]

Clinical presentation of *C. krusei* differed according to the underlying condition. Haematological patients had a higher incidence of metastatic lesions than HIV-infected or SOT patients. When we compared patients with *C. krusei* and *C. albicans* fungaemia, we found significant differences in the clinical presentation. *C. krusei* presented more commonly with skin lesions (23% versus 5%; $P = 0.05$) or other septic metastases (23% versus 5%; $P = 0.05$). Other authors have also found a high proportion (37%) of disseminated infections when *C. krusei* fungaemia is detected in cancer patients.[5] However, the significantly higher proportion of patients with skin lesions among *C. krusei* infections may have been influenced by the different underlying conditions in the two groups, since other *Candida* species have also been described to cause skin dissemination in neutropenic patients.

The portal of entry of *C. krusei* fungaemia was different from that of the *C. albicans* patients. Vascular catheter-related fungaemia predominated in *C. albicans* cases (41% versus 0%; $P = 0.006$) and primary fungaemia in those caused by *C. krusei* (69% versus 20%; $P = 0.001$), which suggests that the gastrointestinal tract was the most probable source. However, GI-tract colonization data were not available.

All our *C. krusei* isolates were intrinsically fluconazole-resistant, the amphotericin B MIC_{90} was 1 mg/L and the voriconazole MIC_{90} was 0.12 mg/L. In our study, eight patients received amphotericin B for therapy (two deaths). *C. krusei* has been reported to cause breakthrough fungaemia during treatment with fluconazole or ketoconazole,[30] even in patients treated with amphotericin B (0.3–0.5 mg/kg per day for a mean of 13 days).[5]

Some authors have suggested that *C. krusei* may be less virulent than *C. albicans*, but in most series *C. krusei* has a higher mortality than the other species.[5,7,13] Mortality is particularly high in patients with persistent fungaemia, persistent neutropenia and septic shock.[5,8]

We could not find significant differences regarding therapy and evolution between *C. krusei* and *C. albicans* fungaemia. The overall mortality rate of *C. albicans* fungaemia was 49% and for *C. krusei*, it was 38% ($P = 0.2$). Our analysis of both *C. albicans* and *C. krusei* fungaemia revealed that the underlying conditions that were poor prognostic factors were the presence of bladder and intravenous catheters and septic shock.

The limitations of our study are that only *C. albicans* and *C. krusei* were compared and that we could not match patients by the presence of neutropenia, since *C. albicans* has completely disappeared from haematological patients in our centre, probably due to the use of prophylaxis.

In summary, our study suggests that the evolution of *C. krusei* fungaemia may be stable in the overall perspective of non-selected units for the care of cancer patients. Clinical hints enable it to be distinguished from *C. albicans* fungaemia and, at

least in our experience, mortality is comparable to that caused by *C. albicans* fungaemia.

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