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Increased Incidence of Fungemia Caused by *Candida krusei*

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***Candida krusei* colonized 12.4% of 868 patients undergoing episodes of therapy-induced granulocytopenia over a 9-year period. The gastrointestinal tract was most frequently colonized, followed by the respiratory tract and urinary tract. Ten patients developed systemic infections with *C. krusei*; all 10 had two or more positive blood cultures. Nine of the 10 patients were colonized with *C. krusei*, and 6 were receiving systemic antifungal agents at the time of development of the infection. Seven patients died within 1 month of *C. krusei* sepsis; systemic candidiasis was seen in the autopsies of the four patients on whom autopsies were performed. Therefore, *C. krusei* should be recognized as an emerging pathogen in select patient populations.**

Candida species and other yeasts are the major cause of fungemia and systemic fungal infections in compromised patient populations. Recent reports suggest that shifts have occurred in the distribution of the infections caused by specific species. Although *Candida albicans* remains the most frequent cause of fungemia (1, 6, 8, 9, 11, 14), there has been an increase in infections caused by *Candida tropicalis* (1, 6, 8, 13) and *Candida parapsilosis* (6, 9). A cluster of infections caused by *Candida krusei* at our institution and a recent report (6) suggesting that *C. krusei* is an emerging pathogen prompted us to review *C. krusei* colonization and infection in patients undergoing prolonged granulocytopenia.

MATERIALS AND METHODS

Patient populations. All patients admitted to the Oncology Center of The Johns Hopkins Medical Institutions, Baltimore, Md., from 1 January 1977 to 31 December 1985 for either bone marrow transplantation or intensive time-sequential chemotherapy for hematologic malignancies were included in this study. A total of 868 patients receiving 1,370 admissions for therapy were evaluated.

The patients were hospitalized in single rooms with high-efficiency particulate air filters (pore diameter, 0.3 μm) that generated 28 to 36 nonlaminar air exchanges per h. All patients received chemotherapy which induced a period of profound granulocytopenia (<100/mm^3) of at least 2 weeks. All patients were given platelet and blood component transfusions, and some received leukocyte transfusions. All patients received systemic antibacterial antibiotics empirically for infectious fever, and some received antifungal prophylaxis with intravenous miconazole. The patients who developed fever refractory to antibacterial antibiotics received empiric amphotericin B (AmpB) with discontinuation of the miconazole.

Fungal cultures. Surveillance cultures of urine, stool or rectal swab, and respiratory (throat) specimens were performed twice a week for the duration of hospitalization. The specimens were cultured on Sabouraud dextrose agar (BBL Microbiology Systems, Cockeysville, Md.) with gentamicin (100 μg/ml). The cultures were incubated at 25°C and examined three times per week for 2 weeks. Specimens from sites of suspected fungal infection were examined microscopically and cultured by standard mycologic procedures.

All yeasts recovered were identified to the species level by germ tube production in human serum, morphology on cornmeal agar (BBL) with Tween 80, fermentation reactions in peptone-yeast extract broth, assimilation reactions, and urease production. The criteria for the identification of *C. krusei* were the absence of germ tube production, the fermentation and assimilation of only glucose, production of characteristic hyphae and blastospores, and weak or absent urease activity. Many isolates were also tested for growth at 42°C to exclude *Candida lambica*, which does not grow at this temperature.

The isolates were tested within 1 week of recovery for susceptibility to AmpB. An agar dilution procedure was used for the testing as previously described (5). Susceptibility for an isolate was defined by an MIC of <2.0 μg/ml.

Systemic infections. Systemic infection was defined by the presence of two or more blood cultures positive for *C. krusei* collected within a 72-h period during granulocytopenia or the recovery of the organism plus histopathologic findings consistent with candidiasis from tissues obtained at biopsy or autopsy. Autopsy findings were reviewed for all patients with antemortem-documented systemic infection and all patients who died within 3 weeks from the date of any culture positive for *C. krusei*.

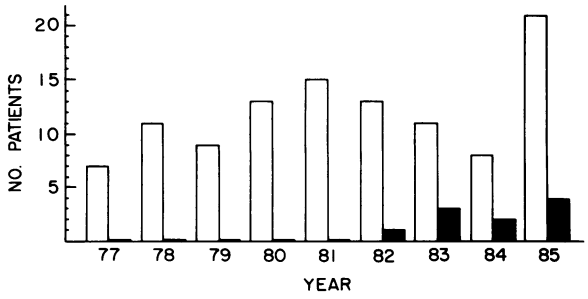

FIG. 1. Colonization and infection of 868 compromised patients with *C. krusei*. Open bars, Colonized patients; solid bars, infected patients.

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TABLE 1. Systemic infections caused by *C. krusei*

Yr	Patient sex and age (yr)	Underlying illness[a]	Colonization before infection	Fungemia			Presepsis therapy	Postsepsis therapy	Outcome after last positive blood culture	Autopsy findings
				Day during aplasia	No. of positive blood cultures	Duration (no. of days)				
1982	Female, 57	Acute erythroleukemia	GI and respiratory tract	15	3	4	Miconazole (16.8 g)	AmpB (667 mg); 5-flucytosine (19 g)	Death (9 days)	Not performed
1983	Female, 32	AML (autologous bone marrow transplant)	None (GI tract 4 days later)	13	5	5		AmpB (896 mg); 5-flucytosine (8 g)	Death (11 days)	Not performed
1983	Female, 24	AML (bone marrow transplant)	GI and respiratory tract	Not aplastic (GVH)[b]	8	4	Miconazole (24.1 g); AmpB (494 mg)	AmpB (217 mg)	Death (1 day)	Candidiasis (lungs and liver)
1983	Female, 50	AMOL	GI, respiratory, and urinary tract	8	2	2		AmpB (165 mg)	Death (2 days)	Candidiasis (lungs and spleen)
1984	Female, 32	AML (bone marrow transplant)	Respiratory tract	11	6	10	Miconazole (21 g)	AmpB (1,504 mg)	Death (17 days)	Not performed
1984	Male, 46	AML	GI tract	40	3	2	Miconazole (16 g); AmpB (960 mg)	AmpB (857 mg)	Death (30 days)	Candidiasis (esophagus and lungs)
1985	Male, 72	AMMOL	GI tract	21	6	4	AmpB (105 mg)	AmpB (1,807 mg); 5-flucytosine (15 g)	Death (4 mo)	Not performed
1985	Female, 65	AMMOL	GI, respiratory, and urinary tract	25	2	3	AmpB (392 mg)	AmpB (1,736 mg); 5-flucytosine (200 g)	Survival (6 mo)	
1985	Male, 60	AMMOL	GI tract	24	4	10		AmpB (4,400 mg); 5-flucytosine (261 g)	Survival (4 mo)	
1985	Male, 42	AML (bone marrow transplant)	Respiratory tract	10	9	6		AmpB (932 mg)	Death (0 days)	Candidiasis (kidney, liver, lungs, and spleen)

[a] AML, Acute myelogenous leukemia; AMOL, acute monocytic leukemia; AMMOL, acute myelomonocytic leukemia.
[b] GVH, Graft-versus-host disease.

RESULTS

Colonization data. The incidence of colonization of the 868 patients over the 9 years is shown in Fig. 1. *C. krusei* was recovered from a total of 108 (12.4%) patients during this 9-year study. Only 46 patients had persistent colonization, defined as two or more surveillance cultures positive for *C. krusei*. The gastrointestinal (GI) tract was the site most commonly colonized (79 patients), followed by the upper respiratory tract (42 patients), and only 7 patients had colonization of the urinary tract. The number of patients colonized each year ranged from 8 to 21. All *C. krusei* isolates recovered from the surveillance cultures were susceptible to AmpB at MICs of ≤ 1.0 μg/ml. The geometric mean MICs for 68 *C. krusei* isolates recovered in 1984 and 1985 was 0.74 μg/ml, whereas the geometric mean MIC for 501 *C. albicans* isolates from the same patient population was 0.40 μg/ml ($P = <10^{-6}$).

Systemic infections. Ten patients had *C. krusei* fungemia (Table 1): all 10 had two or more positive blood cultures within 72 h. No patient had only one positive blood culture. All 10 patients were colonized with *C. krusei*; 9 had positive surveillance cultures before the occurrence of systemic infection (six respiratory, eight GI, and two urinary tract). The number of positive blood cultures per patient ranged from two to nine (mean, 4.8) with the duration of fungemia ranging from 2 to 10 days (mean, 5.0 days). Fungemia occurred at a mean of 23.3 days after the start of chemotherapy or after 16.7 days of granulocytopenia. One patient also had a biopsy of a skin nodule positive by culture and histopathology. Although all patients had indwelling intravascular catheters, none of the infections appeared to be catheter related. All *C. krusei* isolates recovered from blood specimens were susceptible to AmpB. A review of postmortem examinations of all patients colonized with *C. krusei* on whom autopsies were performed did not reveal any additional cases of systemic infection.

Eight of the 10 patients who developed *C. krusei* sepsis had evidence of GI colonization, and all 10 had evidence of GI damage. There was evidence of GI mucosal barrier breakdown associated with significant GI bleeding or enteritis or both thought to be due to either drug toxicity or graft-versus-host disease before or concomitant with fungemia.

All the patients were receiving broad-spectrum antibacterial antibiotics at the time of fungal sepsis, with 6 of the 10 patients receiving broad-spectrum cephalosporins in addition to aminoglycosides or antipseudomonal penicillins or both for specific coverage of a gram-negative pathogen. Six of the 10 patients were also receiving systemic antifungal agents at the time sepsis occurred, and all received AmpB after positive blood culture results. Seven of the 10 patients infected with *C. krusei* died within 1 month of sepsis. Evidence of invasive *C. krusei* infection was detected in all four patients who had positive antemortem blood cultures and on whom autopsies were performed. Histology and cultures were positive for tissue in all four cases. In two of the four patients (a 24-year-old female and a 42-year-old male), the *C. krusei* infection contributed to the cause of death.

DISCUSSION

C. krusei colonized 12.4% of granulocytopenic patients undergoing chemotherapy for hematologic malignancies or bone marrow transplantation. In terms of frequency of colonization, this places *C. krusei* behind *C. albicans*, *C. tropicalis*, *Torulopsis (Candida) glabrata*, and *C. parapsilosis* in this type of patient population (7, 10). Colonization of both the upper respiratory tract and the GI tract occurred more frequently than urinary tract colonization: 39, 73, and 6%, respectively. The colonization data showed an increase in the rate of colonization of the GI tract compared with data from our 1980 report (10) and the experience of another cancer institute (7). The number of patients colonized with *C. krusei* ranged from 8 to 21 from 1977 to 1985.

The emergence of *C. krusei* as a pathogen since 1982 in this patient population, although colonization occurred each year since 1977, may be related to several factors. The well-recognized predisposition to fungal infection in the clinical setting of intensive bone marrow aplasia-inducing chemotherapy is likely a result of profound prolonged granulocytopenia, the use of broad-spectrum antibacterial antibiotics, and damage to the GI mucosa from the presence of tumor infiltrates or from the cytotoxic antitumor agents themselves (3, 12). The destructive effects of intensive cytotoxic drug dose and scheduling (3, 4) on the GI mucosa in particular may facilitate the systemic spread of colonizing organisms. Such mucosal barrier damage, in combination with the increased depth and duration of granulocytopenia induced by intensive antileukemia therapy, likely predisposes to the occurrence of GI tract-related fungal sepsis. All 10 patients with systemic infections had inordinate GI toxicity. Additionally, the empiric use of broad-spectrum antibiotics to reduce mortality from overwhelming gram-negative infection during marrow aplasia and particularly the use since 1982 of broad-spectrum cephalosporins, which are partially excreted in the GI tract (2), may further permit overgrowth by yeasts. Because 6 of the 10 patients had respiratory colonization before sepsis, a respiratory portal of entry cannot be excluded. In addition, there has been a tendency toward the earlier use of antifungal agents, including empiric AmpB and prophylactic miconazole. *C. krusei* may then selectively persist and cause sepsis even during the use of empiric AmpB, due to the relatively high MIC of AmpB for the organism; 6 of the 10 patients infected with *C. krusei* developed fungemia while receiving systemic AmpB or miconazole. Therefore, *C. krusei* should be recognized as an emerging pathogen in the granulocytopenic patient.

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