Breakthrough *Candida tropicalis* Fungemia during Ketoconazole Prophylaxis in Cancer Patients

V. Krcmery Jr., D. Sejnova and E. Pichnova

From the St. Elisabeth and Pediatric National Cancer Institute, Bratislava, Medical School, University of Brno (D. Sejnova, V. Krcmery), CR University of Trnava School of Public Health Trnava (E. Pichnova), Slovakia

Correspondence to: Professor Dr V. Krcmery Jr., St. Elisabeth and Pediatric National Cancer Institute, Heydukova 10, 812 50 Bratislava, Slovakia

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Among 121 adult and pediatric patients from an 8-year fungemia survey conducted at the National and Pediatric Cancer Insititute (Adult and Pediatric Cancer Centers of the Postgradual School and NCI) 6 (5%) cases of *Candida tropicalis* fungemia were observed. In these 6 cancer patients fungemia occurred during prophylaxis with ketoconazole (days 3–5 of prophylaxis with 200 mg bid) (see Table 1). Five out of 6 patients had an inserted central venous line, prior to onset of fungemia. All but one patient had received a combination of third-generation cephalosporin and aminoglycosides, for 3–16 (mean 11) days prior to therapy as well as prophylaxis with oflaxacin for 3–12 days (400 mg once daily orally), one vancomycin and one imipenem. Four out of 6 patients had neutropenia (4–12 days with less than 500 neutrophils per ml of peripheral blood). Single blood cultures were positive in all patients and associated with fever and shivering in 5 out of 6 patients, followed by septic shock with hypotension and death in 3 (50% mortality). Two patients were treated with amphotericin B (1 death) and 4 with fluconazole (2 deaths) with 50% mortality after each treatment regimen.

Three cases of fungemia occurred in children and 3 in adults (Table 1). Compared with the incidence of *C. albicans* (45.5%), *C. krusei* (9%), *C. parapsilosis* (9%) and *C. glabrata* (6.3%), *C. tropicalis* (5% of all fungemia cases in our center) ranked fifth as the most common pathogen. A univariate analysis shows (χ^2 with the help of Fisher's exact test) that *C. albicans* ($n = 51$) and non-albicans fungemia ($n = 32$) occurred at the same time in the same institution (see Table 2). Breakthrough fungemias ($p < 0.01$), especially during ketoconazole prophylaxis ($p < 0.001$), were attributable to overall mortality ($p < 0.001$) as well as being significantly more frequent among *C. tropicalis* cases than other (*C. albicans* or non-albicans *Candida* spp.) fungemia cases.

Furthermore, other large epidemiologic studies in Europe (1) as well as in the US (2, 3) documented that *C. tropicalis* was associated with higher mortality than other non-albicans *Candida* spp. or *C. albicans* (Table 3).

Finally, an association between certain pathogens and antifungal agents was described, suggesting that *C. krusei* and *C. glabrata* could be selected after fluconazole (4, 5) or *Trichosporon* spp. after itraconazole (6) prophylaxis. All 6 *C. tropicalis* fungemia cases occurred after prophylaxis with ketoconazole. There is no other report about such a relationship, except one proposing that patients receiving prophylaxis with ketoconazole during neutropenia had more bacteremia that those without ketoconazole prophylaxis (7). Thus, more data on the role of ketoconazole and other antifungal agents in the selection of particular non-albicans *Candida* spp. or non-*Candida* yeasts are expected.

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Table 1

Fungemia attributable to C. tropicalis. Risk factors and outcome in 6 cases

Age/sex	Underlying disease	CVC	ATB	Neutropenia	Mucositis	Chemotherapy	Corticosteroides	Quinolone prophylaxis	Anti-fungal prophylaxis
6M	Neo retroperi-toneum	+	+	+	−	+	−	+	KET 3
15F	NHL	+	+	+	−	+	+	+	KET 5
14F	CNS s. tumor	+	+	−	−	−	+	−	AmB + KET 5
50F	Solid tumors (GIT)	+	+	+	−	+	+	−	KET 5
45F	Solid tumors (GIT)	+	+	−	−	−	−	−	KET 3
61F	Solid tumor (GIT)	−	−	+	+	+	−	−	KET 3

Abbreviations: RT = retroperitoneal tumour, ST = solid tumour, CNS = central nervous system, CVC = central venous catheter, NHL = non-Hodgkin's lymphoma, ATB = antibiotics, KET = ketoconazole, AmB = amphotericin B, FLU = fluconazole.

Table 2

Comparison of C. Tropicalis to C. albicans and non-albicans Candida spp.: risk factors and outcome

	C. albicans n = 51 (A)	Non-albicans *Candida* spp. n = 32 (B)	*C. tropicalis* n = 6 (C)	P (AC)	P (BC)
Mucositis	12 (23.5)	5 (15.6)	3 (50)	NS	NS
Two and more positive blood cultures	6 (11.8)	2 (6.3)	0 (0)	NS	NS
Acute leukemia	6 (11.8)	5 (15.6)	0 (0)	NS	NS
Neutropenia	21 (41.2)	15 (46.8)	4 (66.6)	NS	NS
Previous ATB Th.	46 (92)	19 (54.4)	5 (84.3)	NS	NS
Catheter insertion	40 (73.4)	24 (75)	5 (84.3)	NS	NS
Th. with corticosteroides	14 (27.5)	9 (28.1)	3 (50)	NS	NS
Prophylaxis with quinolones	13 (25.5)	9 (28.1)	2 (33.3)	NS	NS
Breakthrough fungemia during prophylaxis with:	20 (39.2)	13 (40.6)	5 (84.3)	0.01	0.01
Fluconazole	1 (2.0)	3 (9.4)	0	NS	NS
Ketoconazole	5 (9.8)	6 (18.8)	5 (84.3)	0.001	0.001
Itraconazole	3 (5.8)	3 (9.4)	0	NS	NS
Amphotericin B	11 (21.6)	4 (12.5)	0	0.001	NS
Catheter-associated fungemia	6 (11.8)	4 (12.5)	1 (10)	NS	NS
Organ complications	10 (19.6)	7 (21.8)	3 (50)	NS	NS
Therapy with AmB/deaths	23/6 (26.1)	16/8 (50)	1/2 (50)	NS	NS
Therapy with FLU/deaths	26/5 (19.2)	13/4 (30.8)	2/4 (50)	NS	NS
Cure	39 (76.5)	19 (59.4)	3 (50)	0.02	NS
Death due to fungemia (attributable mortality)	7 (15.7)	8 (25.0)	3 (50)	0.001	0.05
Death due to underlying diseases with fungemia	5 (9.8)	5 (15.6)	3 (50)	0.001	0.02
Overall mortality	12 (25.5)	13 (40.6)	3 (50)	0.03	NS

Risk factors and outcome in 6 cases

Organism	No. of posit.	Therapy			Outcome	Complications	Source of fungemia	Comments
		Drug	Length of Th.	Total dose				
C. tropicalis	1	FLU	10	1 g	Cured	None	Unknown	Break-through
C. tropicalis 1	1	AmB	10	0.5 g	Death	Shock	Unknown	Break-through
C. tropicalis	1	FLU	21	4.2 g	Death	Meningitis	CNS	Break-through
C. tropicalis	1	FLU	13	2.6 g	Cured	None	Unknown	–
C. tropicalis	1	AmB	2	0.5 g	Death	Death	Unknown	–
C. tropicalis	1	FLU	16	2.0 g	Cured	None	Unknown	–

Table 3

C. tropicalis fungemia in cancer patients, data from 6 studies in cancer patients only

	No. of fungemias	*C. tropicalis* fungemias	Mortality	Risk factors, statistical significance
Wingard (3) US	1 591	23%	ND	Leukemia, higher virulence, ATB therapy
Abi Said (2) US	491	18%	ND	Early onset, neutropenia
Viscoli (1) Eur.	324	15%	45%	Mortality
Krcmery, V Jr. (6) (current study)	101	6%	50%	Antifungal prophylaxis with ketoconazole, mortality
White (8)	32	28%	56%	None
Lecciones (9)	155	13%	ND	Vascular catheter insertion

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