

Non-albicans Candida Species in Cancer Patients

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E. Dorko, M. Kmetová, E. Pilipčinec, F. Dorko, I. Bračoková, A. Marossy, I. Škardová: Non-albicans Candida species in cancer patients. The authors analyze incidence of non-albicans Candida species and non-Candida species isolated from cancer patients. The results of examination shown that presence of 9 non-albicans Candida spp. and non-Candida spp.: *C. parapsilosis* (n=20), *C. tropicalis* (n=9), *C. krusei* (n=4), *Cr. neoformans* (n=2), *C. clausenii*, *C. intermedia*, *C. mogii*, *C. pulcherrima* and *C. zeylanoides* (n=1 each). Classifying the sample according to the patient's diagnosis, the yeasts were most frequently isolated from patients with leukemia (n=14), with non-specified cerebral tumor (n=6), Hodgkin's disease (n=3), squamous cell carcinoma of oral cavity (n=3), myeloma (n=2), and other neoplastic diseases (lymphoma, non-specified tumor of larynx, nasal cavity and middle ear, colon tumor, non-Hodgkin's lymphomas, breast cancer). Regarding the localization of samples in which the above yeasts were detected, most frequently the positive samples were found in swabs taken from oropharyngeal region (n=11) and blood (n=10).

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Introduction

One of the major problems in therapeutic management of cancer patients is invasive fungal infection (De Pauw, 1997). These infections are responsible for more than 40% of the total number of deaths (Kalin and Petrini, 1996). The increased number of reports on cancer patients with serious systemic infections caused by new or rare fungal pathogens could be due to new therapeutic regime. At the same time this increase could be ascribed to increased percentage of diagnosed clinical infections by physicians and microbiologists (Krčmery, 1996). In the course of last two decades we have seen increased incidence of fungal infections due to various factors such as: AIDS pandemic, increased utilization of myelotoxic chemotherapy and organ transplantation, prolonged usage of wide-spectrum antibiotics and aggressive intensive care methods (Antrum, 1996). In cancer patients the main risk factors for development of systemic fungal infection include: prolonged neutropenia, mucosal injury, presence of central venous catheters, immunosuppressive therapy and others (Anaissie *et al.*, 1998, Herbrecht, 1996, Královicová *et al.*, 1997). The *Candida* species is most frequently isolated from neutropenic patients. Even though *C. albicans* is a predominant yeast, other species specified as non-albicans *Candida* e.g. *C. glabrata*, *C. krusei* are frequently found in cancer patients and possibly reflect the extended use of fluconazole to which these species are resistant (Herbrecht, 1996).

Improvement of existing diagnostic methods and introduction of new ones (PCR) allowed rapid and accurate identification of genus and species of yeast. Therefore patients with malignancies are more frequently diagnosed not only with *C. albicans* infections but also with other non-albicans *Candida* spp. considered to be commensals or facultative pathogens. In our work we want to discuss incidence of wide range of yeasts other than *C. albicans* in cancer patients.

Materials and Methods

Samples of clinical material such as oropharyngeal swabs (n = 11), blood (n = 10), samples taken from the surface from catheters and endotracheal tubes (n = 6 each), wound swabs, urine (n = 2 each), smear from skin, vaginal swab and cerebrospinal fluid (n = 1 each) were obtained from patients hospitalized in the University Hospital in Košice.

Yeasts were identified (1) through microscopic examination by Gram staining, (2) by cultivation on Sabouraud dextrose agar (Imuna, Slovakia) and on CHROMagar *Candida* (Mast Diagnostica, France), (3) by assimilation and fermentation on auxanograms and zymograms (AUXACOLOR, Sanofi Pasteur Diagnostica, France), (4) by germ tube test and (5) on rice agar with Tween 80, where production of mycelium and its branching as well as the shape and size of blastospores and their arrangement were observed (Dorko *et al.*, 1999, Otčenášek *et al.*, 1990) Demographic data such as age, sex and diagnosis were also recorded.

Results

From 40 cancer patients we have identified 9 non-albicans *Candida* spp. and non-*Candida* spp. as follows: *C. parapsilosis* (n = 20), *C. tropicalis* (n = 9), *C. krusei* (n = 4), *Cr. neoformans* (n = 2), *C. clausenii*, *C. intermedia*, *C. mogii*, *C. pulcherrima* and *C. zeylanoides* (n = 1 each) (Table 1). Most frequently detected yeast proved to be *C. parapsilosis* (n = 20) isolated in the

following diagnoses and from the following clinical material: in cases of leukemia from blood (n = 3), endotracheal tubes (n = 2) and nasopharynx (n = 1); in cases of squamous cell carcinoma from nasopharynx (n = 2); in cases non-specified cerebral tumor and lymphoma from endotracheal tubes and catheters (n = 2 each); in case non-specified tumor of the nasal cavity and middle ear from skin; in case of cancer of large intestine from surgical wound; in non-Hodgkin's lymphomas from endotracheal tube; in multiple myeloma and breast cancer from urine and in other malignancies from catheter (n = 2) and blood (n = 1). In relation to the material this pathogen was most frequently detected on devices made of plastic materials such as endotracheal tubes (n = 5) and catheters (n = 4). Other positive samples included

Table 1: Incidence of yeasts in cancer patients

Species	n =	%
<i>C. parapsilosis</i>	20	50
<i>C. tropicalis</i>	9	22,5
<i>C. krusei</i>	4	10
<i>Cr. neoformans</i>	2	5
<i>C. clausenii</i>	1	2,5
<i>C. intermedia</i>	1	2,5
<i>C. mogii</i>	1	2,5
<i>C. pulcherrima</i>	1	2,5
<i>C. zeylanoides</i>	1	2,5

blood (n = 4), nasopharynx (n = 3), urine (n = 2), skin and wound samples (n = 1 each). *C. parapsilosis* was found in 13 adult patients and 7 children resulting in the ratio of 1: 85:1. The adults were diagnosed with the following diagnoses: leukemia, non-specified cerebral tumor, lymphoma, squamous cell carcinoma of oral cavity (n = 2 each), non-specified tumor of nasal cavity and middle ear, cancer of large intestine, non-Hodgkin's lymphomas, multiple myeloma and breast tumor (n = 1 for each). The children was diagnosed with leukemia (n = 4) and unspecified malignancies (n = 3). In the group of adults *C. parapsilosis* was isolated predominantly from males (n = 12), in the group of children from females (n = 6) (Table 2). Average age of adults was 58,9 years (males 60,1; females 44). Average age of children was 10,2 years (females 9,6; males 14).

C. tropicalis was isolated from nasopharynx (n = 2), catheter surface and blood in 4 children with leukemia; from nasopharynx of a girl with Hodgkin's disease and from blood of a girl with multiple myeloma. Five girls were diagnosed the following with primary malignancies: leukemia (n = 3), Hodgkin's disease and multiple myeloma. One boy was diagnosed with leukemia. In this group three strains of *C. tropicalis* were isolated from nasopharynx, two strains from blood and one strain from catheter smear. The average age in this group was 9,6 years (females 9,5; males 10). Further three strains were detected from nasopharynx, blood and endotracheal tube surface samples of adult men (average age 54,6 years) diagnosed with Hodgkin's disease, non-specified cerebral tumor and squamous cell carcinoma of oral cavity. Results point out that high incidence of *C. tropicalis* can be observed in patients with leukemia (n = 4) and in samples taken from nasopharynx (n = 4) in Table 3.

Four (i.e. 10% of the total number) of the yeast isolates consisted of strains of *C. krusei*. They were found in nasopharyngeal sample and catheter surface sample from

patients with leukemia and in cerebrospinal fluid of patient with non-specified cerebral tumor. This group of patients included two boys and one girl. The average age in this group was 8,1 years (males 8,5; females 6). The adult patient was 58 years old man with multiple myeloma and with positive haemoculture of *C.krusei* (Table 3).

Non-Candida spp. yeasts were represented by two isolates of *Cr.neoformans* from oral cavity of one patient with leukemia and one patient with Hodgkin's disease. They were male patients with average age of 55 years (Table 4).

Occurrence of other non-albicans Candida spp. in regard to material, diagnosis, age and gender was: *C.claussenii*, nasopharynx, non-specified cerebral tumor, 6 years old female; *C.intermedia*, vagina, carcinoma in situ, 29 years old female; *C.mogii*, blood, leukemia, 6 years old female; *C.pulcherrima*, blood, non-specified cerebral tumor, 5 years old female; *C.zeylanoides*, surgical wound, laryngeal carcinoma, 54 years old male (Table 4).

The above results lead us to the following conclusion: non-albicans Candida spp. and non-Candida spp. most frequently occur in patients with following diagnoses: in 14 patients with leukemia (*C.parapsilosis* n=6, *C.tropicalis* n=4, *C.krusei* n=2, *C.mogii*, *Cr.neoformans*); in 6 patients with cerebral tumor (*C.parapsilosis* n=2, *C.claussenii*, *C.krusei*, *C.pulcherrima*, *C.tropicalis*); in 3 patients with Hodgkin's disease (*C.tropicalis* n=2, *Cr.neoformans*); in 3 patients with multiple myeloma (*C.krusei*, *C.parapsilosis*, *C.tropicalis*); in 3 patients with squamous cell carcinoma of oral cavity (*C.parapsilosis* n=2, *C.tropicalis*); in 3 patients with non-specified malignancies (*C.parapsilosis*); in 2 patients with lymphoma (*C.parapsilosis*) and in one with laryngeal carcinoma (*C.zeylanoides*), in patients with non-specified tumor of nasal cavity and middle ear, cancer of large intestine, non-Hodgkin's lymphomas, breast cancer (*C.parapsilosis*) and in a patient with carcinoma in situ (*C.intermedia*) in Tables 1,2,3,4.

Regarding the locations from which the positive samples were obtained, the most frequent location of incidence of yeasts included nasopharynx (11-times, *C.tropicalis* n=4, *C.parapsilosis* n=3, *Cr.neoformans* n=2, *C.claussenii*, *C.krusei*); blood (10-times, *C.parapsilosis* n=4, *C.tropicalis* n=3, *C.krusei*, *C.mogii*, *C.pulcherrima*); endotracheal tubes (6-times, *C.parapsilosis* n=5, *C.tropicalis* n=1); catheters (6-times, *C.parapsilosis* n=4, *C.krusei*, *C.tropicalis*); wound (2-times, *C.parapsilosis*, *C.zeylanoides*); urine (2-times, *C.parapsilosis*); vaginal sample (*C.intermedia*) and liquor (*C.krusei*) in Tables 1,2,3,4.

As far as distribution by gender is concerned, the yeasts were recorded in 23 male patients (19 adult and 4 boys) and in 17 females (15 girls and 2 adult women); in men *C.parapsilosis* (12 adult men, one boy), *C.tropicalis* (3 adult men, 1 boy), *C.krusei* (2 boys, 1 adult man), *Cr.neoformans* (2 adult men), *C.zeylanoides* (adult man); in women *C.parapsilosis* (6 girls, adult woman), *C.tropicalis* (5 girls), *C.krusei* (girl), *C.claussenii* (girl), *C.intermedia* (adult woman), *C.mogii* (girl), *C.pulcherrima* (girl) in Tables 1,2,3,4.

Discussion

Various authors have been discussed the increased incidence of fungal infections in cancer patients. Non-albicans Candida spp. are to be considered a main cause of candidaemia 89% in cancer patients as presented by Nucci *et al.* (1998). *C.parapsilosis* was the most frequent species of non-albicans

Candida found in cancer patients. Krčmery *et al.* (1998) pointed out the increased frequency of *C.parapsilosis* fungaemia associated with intravascular catheters from 7,1% in 1996 up to 15% in 1997. We have isolated this pathogen frequently in smears from endotracheal tubes and catheters (n=9) and from blood (n=4). *C.parapsilosis* is an important nosocomial pathogen capable proliferation in solutions with light content glucose and is also able to produce bio-films on prosthetic materials from which catheters, endotracheal tubes, cardiac valves and other devices are made (Branchini *et al.*, 1994). Incubation and insertion of intravascular catheters for reason of application of drugs and parenteral nutrition are all common therapeutic methods in patients in critical condition and in coma such as patients with neoplastic diseases. Adherence of *C.parapsilosis* to the surface of these devices directly contributes to multi-fold increase of *C.parapsilosis* Candidaemia cases.

We detected *C.tropicalis* from nasopharynx (n=4, i.e. 10%), from blood (n=3, i.e. 7.5%) and from prosthetic materials (n=2, i.e. 5%). *C.tropicalis* was described as one of the main cause of candidosis caused by non-albicans Candida spp. and was isolated in 48% of blood cultures obtained from cancer patients (Abi-Said *et al.*, 1997; Nucci *et al.*, 1998). A disagreement with these results, Krčmery *et al.* (1998) reported only one case of *C.tropicalis* in a group of 41 patients. 18% occurrence of *C.tropicalis* was reported in samples taken from oral cavity of HIV positive patients with symptoms of oropharyngeal candidosis (Rodero *et al.*, 1997). Similar to *C.parapsilosis*, *C.tropicalis* has a capability to adhere PVC materials, silicon prostheses, and shows a certain degree of thigmotropism. These properties facilitate occurrence of fungaemia. Adherence is facilitated by the surface integrins (Nikawa *et al.*, 1997).

C.krusei was detected in increased numbers of patients having undergone bone marrow transplantation and in immunocompromised patients. It is responsible for 1 - 4 % infections in cancer patients (Abi-Said *et al.*, 1997; Wingard, 1995). In clinical practice a reduction of the number of infections induced by *C.albicans* and *C.tropicalis* has been observed. On the other hand an increase number of infections induced by *C.krusei* has been observed. This change is linked with widespread usage of triazole drug based on fluconazole to which the mentioned yeast is resistant (Berrouane *et al.*, 1996). Anaissie *et al.* (1998) discovered a coincidence of fluconazole therapy and *C.krusei* infections in up to 33% cases. Venkateswarlu *et al.* (1996) also presented the acquired resistance to itraconazole and ketoconazole. Španik *et al.* (1995) described fungaemia associated with catheter use in patients suffering from leukemia undergoing prophylactic treatment by itraconazole. Both the blood cultures and a sample from the tip of catheter removed from jugular vein were *C.krusei* positive. We have isolated *C.krusei* in four cases, i.e. in 10% of all cases from different clinical material (catheter, blood, liquor, nasopharyngeal samples). This, however is significantly less than reported by Kunová *et al.* (1995) (up to 21,2%) but our results are very similar to the results of Krčmery *et al.* (1998) (3/41 i.e. 7,3%).

One of the interesting findings of our study was the absence of *C.glabrata*. In publications of Wingard (1995), Abi-Said *et al.* (1997) and Anaissie *et al.* (1998) *C.glabrata* was the third most frequent pathogen (following *C.tropicalis* and *C.parapsilosis*) but also other authors detected this yeast

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Table 2: Incidence of *C.parapsilosis* in clinical material in relation to diagnosis and sex

Species	Diagnosis	(n=)	Material	(n=)	Sex
<i>C.parapsilosis</i>	leukemia	6	blood	3	2 F, M
			E.T.	2	M,F
			nasopharynx	1	M
	squamous cell carcinoma	2	nasopharynx	2	2M
			lymphoma	2	M
	tumor of nasal cavity and middle ear	1	E.T.	1	M
			catheter	1	M
	cancer of large intestine	1	skin	1	M
			wound	1	M
	non-Hodgkin's lymphomas	1	E.T.	1	M
			multiple myeloma	1	M
	breast cancer	1	urine	1	M
			urine	1	F
	non-specified malignancies	3	catheter	2	2F
			blood	1	F
cerebral tumor	2	E.T.	1	M	
		catheter	1	M	

Note: F, female, M, male; E.T., endotracheal tube

Table 3: Incidence of *C.tropicalis* and *C.krusei* in clinical material in relation to diagnosis and sex

Species	Diagnosis	(n=)	Material	(n=)	Sex
<i>C.tropicalis</i>	leukemia	4	nasopharynx	2	2F
			catheter	1	F
			blood	1	M
	Hodgkin's disease	2	nasopharynx	1	F
			E.T.	1	M
			multiple myeloma	1	F
squamous cell carcinoma	1	nasopharynx	1	M	
		cerebral tumor	1	M	
<i>C.krusei</i>	leukemia	2	nasopharynx	1	F
			catheter	1	M
	cerebral tumor	1	liquor	1	M
			multiple myeloma	1	M

Note: F, female, M, male; E.T., endotracheal tube

Table 4: Incidence of *Cr.neoformans*, *C.claussenii*, *C.intermedia*, *C.mogii*, *C.pulcherrima* and *C.zeylanoides* in clinical material in relation to diagnosis and sex

Species	Diagnosis	(n=)	Material	(n=)	Sex
<i>Cr.neoformans</i>	leukemia	1	nasopharynx	1	M
	Hodgkin's disease	1	nasopharynx	1	M
<i>C.claussenii</i>	cerebral tumor	1	nasopharynx	1	F
<i>C.intermedia</i>	carcinoma in situ	1	vagina	1	F
<i>C.mogii</i>	leukemia	1	blood	1	F
<i>C.pulcherrima</i>	cerebral tumor	1	blood	1	F
<i>C.zeylanoides</i>	laryngeal carcinoma	1	wound	1	M

Note: F, female, M, male

microorganism from cancer patients (De Pauw, 1997, Herbrecht, 1996, Krcmery *et al.*, 1998, Kunová *et al.*, 1995). Until 1980 occurrence of cryptococcosis was recorded only sporadically, but with AIDS pandemic the number of cryptococcosis infections increased. Typical cases of cryptococcosis occurred in patients with immune system dysfunction as in the case of patients with Hodgkin's disease and leukemia as was confirmed also in our work (Korfel *et al.*, 1998).

We have also isolated one strain of each: *C.claussenii*, *C.intermedia*, *C.mogii*, *C.pulcherrima* and *C.zeylanoides* in cancer patients. They were isolating other strains such as *C.guilliermondii*, *C.lusitaniae*, *C.pseudotropicalis*, *C.kefyr*.

The yeasts were most frequently cultivated (n = 12, i.e. 33%) from catheters and endotracheal tubes. Use of catheters and endotracheal tubes is considered to be a significant risk factor of fungaemia in patients with cancer (Abi-Said *et al.*, 1997; Anaissie *et al.*, 1998; Branchini *et al.*, 1994; De Pauw, 1997; Herbrecht, 1996; Královicová *et al.*, 1997; Krcmery *et al.*,

1998; Nikawa *et al.*, 1997, Nucci *et al.*, 1998, Španik *et al.*, 1995; Wingard, 1995).

We detected 9 non-albicans Candida spp. and non-Candida spp. in cancer patients. The most frequent yeast was *C.parapsilosis* in leukemic patients. Other isolated fungal microorganisms were: *C.tropicalis*, *C.krusei*, *Cr. neoformans*, *C.claussenii*, *C.intermedia*, *C.mogii*, *C.pulcherrima* and *C.zeylanoides*.

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