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Identification of *Candida* spp. in the oral cavity in patients with malignant diseases

Identifikacija vrsta gljivica iz roda *Candida* u usnoj duplji bolesnika sa malignim oboljenjem

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Abstract

Background/Aim. Oral candidiasis frequently causes discomfort in patients treated for malignant diseases, acting as well as a potential source of systemic infection. This disease may present itself through different clinical manifestations of both acute or chronic type. The aim of this study was to identify different *Candida* species from oral cavities of patients suffering from malignant diseases. **Methods.** Thirty patients admitted to the hospital for diagnostics/treatment of malignant diseases were included in this investigation. All subjects had visible changes of oral mucosa in the form of pseudomembranes and inflammation corresponding to oral candidiasis. Control group included 30 non-hospitalized patients diagnosed with candidiasis. Diagnosis of oral candidiasis was confirmed in all patients by microbiological analysis of tongue swabs. For microbiota identification, three different tests were used: germination test, fungal growth test on corn meal agar, and biochemical identification with commercially available ID 32 C kit (bio-Merieux, Marcy-l'Étoile, France). **Results.** Out of 30 isolates collected from hospitalized patients, 90% was related to *Candida albicans*, 7% was identified as *Candida kefyr*, and 3% as *Candida famata*. In samples collected from non-hospitalized controls, we isolated *Candida albicans* in 90% of the cases, in 7% *Candida kefyr*, while in 3% we identified *Candida glabrata*. **Conclusion.** Based on this investigation, oral candidiasis in patients treated with radiotherapy and chemotherapy is mainly caused by *Candida albicans*. It is to be expected that *Candida albicans* will remain the most significant causative agent of oral candidiasis, although we must bear in mind the possibility of other pathogenic species.

Key words:

candida; candida albicans; mouth; neoplasms; microbiological techniques; candidiasis, oral.

Apstrakt

Uvod/Cilj. Oralna kandidijaza čest je uzročnik nelagodnosti kod bolesnika na terapiji zbog malignih bolesti, a može biti i potencijalni izvor sistemskih infekcija. Bolest se može manifestovati kroz različite kliničke slike, koje mogu poprimiti akutni ili hroničan tok. Cilj ovog rada bio je da se identifikuju *Candida* iz usne duplje bolesnika sa malignim bolestima. **Metode.** U istraživanje je bilo uključeno 30 bolesnika hospitalizovanih zbog maligne bolesti. Svi ispitanici imali su promene na oralnoj sluzokoži, sa pseudomembranama i upalom, odnosno s kliničkim izgledom oralne kandidijaze. Kontrolnu grupu ispitanika sačinjavalo je 30 nehospitalizovanih bolesnika koji su imali kliničku sliku kandidijaze. Kod svih ispitanika sprovedena je mikrobiološka obrada brisa oralne sluzokože sa jezika, koja je potvrdila dijagnozu oralne kandidijaze. U svrhu identifikacije korišćena su tri testa: test klijanja, test rasta kvasaca na kukuruznom agaru i biohemijska identifikacija pomoću komercijalnog testa ID 32 C (*bio-Merieux, Marcy-l'Étoile, France*). **Rezultati.** Od ukupno 30 izolata sakupljenih od 30 hospitalizovanih bolesnika, kod 90% radilo se o vrsti *Candida albicans*, 7% identifikovano je kao *Candida kefyr*, a 3% kao *Candida famata*. U uzorcima sakupljenim od 30 nehospitalizovanih osoba, u 90% bila je izolovana *Candida albicans*, u 7% *Candida kefyr*, a u 3% *Candida glabrata*. **Zaključak.** Na osnovu ovog istraživanja potvrđeno je da je oralna kandidijaza kod bolesnika na radioterapiji i/ili hemoterapiji zbog maligne bolesti najčešće uzrokovana gljivicom *Candida albicans*. Može se očekivati da će *Candida albicans* i dalje biti najznačajniji uzročnik oralne kandidijaze, iako su mogući i drugi uzročnici infekcije.

Ključne reči:

candida; candida albicans; usta; neoplazme; mikrobiološke tehnike; kandidijaza, oralna.

Introduction

Candida species (*Candida* spp.) are constitutive members of oral flora. Nearly half of the healthy adult population has these fungi on the mucosal surface without experiencing any symptoms since the immune system controls its excessive growth and development of the disease^{1,2}. However, in cases of some local and systemic predisposing factors, there is a possibility of oral candidiasis development. The local predisposing factors are changes in salivary gland function, use of antibiotics and corticosteroid drugs, carbohydrate-rich diet, changes in oral epithelium, dentures, or excessive tobacco use. Systemic predisposing factors include changes in hormonal status, iron, folic acid and vitamin B12 deficiencies, use of antibiotics, malignant diseases and immune suppression of different origins³⁻⁵. Oral candidiasis may be manifested through different clinical signs and symptoms, as acute pseudomembranous, acute atrophic candidiasis, chronic atrophic candidiasis, glossitis and angular cheilitis⁴.

Oral candidiasis is the most common opportunistic infection in patients with malignant diseases⁶. Cytotoxic therapy and radiotherapy are both important predisposing factors in its development. Patient's defense mechanisms which have already been weakened by the main disease may be further depleted by cytotoxic and radiation therapy^{6,7}. As a consequence of cytotoxic therapy, oral candidiasis occurs in 30–70% of the patients⁸. Side effects of head and neck radiotherapies, such as dry mouth and thick sticky saliva, are coupled with an increased colonization of oral mucosa with *Candida*, especially *Candida albicans* (*C. albicans*). Such milieu favors the development of oral candidiasis in 17% to 52.5% of the patients^{6,7,9}. Fungi belonging to *Candida* spp. are responsible for 75% of all fungal infections in patients with malignancies. According to the literature, *C. albicans* is isolated in 70–80% of all patients, while *Candida glabrata* (*C. glabrata*) and *Candida tropicalis* (*C. tropicalis*) appear in 5–8% of the cases. Recent research shows an increase in trend of non-*albicanscandidal* infections (*C. glabrata*, *C. parapsilosis* and *C. tropicalis*), while the share of *C. albicans* decreased⁹.

Development of oral candidiasis in patients treated with radiotherapy and chemotherapy presents a significant factor for the systemic infection and candidaemia which may act as a direct cause of death¹⁰⁻¹². The European Organization for Research and Treatment of Cancer – International Antimicrobial Therapy Group published the data of oral cavity being the source of 23% of the microorganisms isolated from the blood of neutropenic patients with carcinoma¹³.

The purpose of this study was to determine the *Candida* species responsible for the development of the disease in patients under cytotoxic therapy and/or radiotherapy for treatment of a malignant disease.

Methods

This research included thirty patients hospitalized at the Clinic of the Internal Medicine and Clinic of Radiology and Oncology, Clinical Hospital Center Rijeka. Table 1 presents demographic and clinical characteristics of hospitalized patients. At the time of sampling, 19 of them were subjected to

cytostatic therapy, while 11 of them went through radiotherapy. All subjects had visible changes in the oral mucosa with pseudomembranes whose clinical appearance corresponded to oral candidiasis. All subjects were microbiologically tested in order to confirm the diagnosis. Patients did not use any antifungal drugs for at least one month before sampling procedures.

The control group was made by 30 patients from the Clinic of Dental Medicine of the same hospital center. All of them had a fully developed scope of clinical signs and symptoms corresponding to oral candidiasis and did not suffer from any malignancy.

Both groups were introduced to the purpose of the research upon the inclusion and by signing the Informed consent agreed to participate. The research had been approved by the Ethics Committee of the Clinical Hospital Center Rijeka.

Cultivation and identification of Candida

Subjects were taken the oral mucosa swabs from the tongue region with a sterile cotton swab (Copan, Zagreb, Croatia). Immediately upon collection, the material was streaked out on solid Sabouraud dextrose agar plates (PanreacQuimica, Cultimed, Spain) and incubated at 37°C for 72 h. Distinctive colonies sized 2–3 mm, with smooth and shiny surface and clean margins, white to cream in color, and with typical yeast smell, were transferred and multiplied on new solid medium plates. Positive strains were identified by standard mycological methods, by germ tube production, chlamyospore development in the microculture in cornmeal Tween 80 (Difco, Detroit, USA) and API ID 32 *Candida* identification kit (bio-Merieux, Marcy-l'Etoile, France). The germ-tube test involved the induction of hyphal outgrowths from yeast cultured in rabbit serum for 3 h at 37°C. Microscopic slides were examined under light microscope. This test was used for *C. albicans* identification. Chlamyospore production was also associated with *C. albicans*. *C. albicans* produced thick-walled, dormant growth forms induced *in vitro* by culture agar supplemented with Tween 80. The inoculated area was covered with the cover slip and the agar incubated at 22°C for 72 h. Under such conditions, cornmeal agar also included a characteristic filamentous growth which could aid in the identification of *C. albicans*. The API ID 32 C system consists of a single use disposable plastic strip with 32 wells containing substrates for 29 assimilation tests (carbohydrates, organic acids, and amino acids), one susceptibility test (cycloheximide), one colorimetric test (esculin), and one negative control. The yeast identification procedures were conducted in accordance with the manufacturer's instructions. One day-cultures and sterile distilled water were used to prepare the suspensions with final turbidity equivalent to McFarland #2. Five drops of this suspension were then dispensed to ampoules of C medium provided by the manufacturer and homogenized to prepare an even dispersion of inoculum. The inoculum suspensions were used to inoculate the wells. The systems were incubated at 30°C for 48 h. The results were visually examined and transformed into numerical bio-codes. At the end, the isolates were identified by ID 32 Analytical Profile Index.

Table 1

Age, gender, type of malignancy and type of therapy in hospitalized group						
Hospitalized patients	Gender	Age (years)	Type of malignancy	Type of therapy		
				surgery	chemotherapy	radiotherapy
1	m	73	Non-Hodgkin lymphoma	-	+	-
2	f	57	Leukemia	-	+	-
3	m	71	Colon cancer	+	+	-
4	f	51	Ovarian cancer	+	+	-
5	m	73	Oral cancer	+	-	+
6	f	55	Breast cancer	+	-	+
7	m	51	Colon cancer	+	+	-
8	m	71	Prostate cancer	+	+	-
9	f	69	Thyroid cancer	+	-	+
10	f	31	Leukemia	-	+	-
11	m	52	Colon cancer	+	+	-
12	m	64	Oral cancer	+	-	+
13	f	51	Breast cancer	+	-	+
14	f	49	Breast cancer	+	-	+
15	f	66	Thyroid cancer	+	-	+
16	f	65	Uterine cancer	+	-	+
17	f	71	Oral cancer	+	-	+
18	m	66	Prostate cancer	+	+	-
19	f	78	Breast cancer	+	-	+
20	f	59	Leukemia	-	+	-
21	f	64	Breast cancer	+	+	-
22	f	69	Colon cancer	+	+	-
23	f	49	Non-Hodgkin lymphoma	-	+	-
24	m	70	Oral cancer	+	-	+
25	f	72	Breast cancer	+	+	-
26	m	58	Gastric cancer	+	+	-
27	f	65	Leukemia	-	+	-
28	f	61	Breast cancer	+	+	-
29	f	54	Colon cancer	+	+	-
30	m	64	Prostate cancer	+	+	-

m – male; f – female.

Statistical analysis

Statistical analysis was performed using the Statistica 12.7 software (StatSoft, Inc., Tulsa, OK, USA)

The Kolmogorov-Smirnov normality test was applied to our data. The Student-*t* test was used to analyze the age difference between groups while the χ^2 test was used to compare the genders. Fisher's exact test was used to analyze oral candida distribution in hospitalized and non-hospitalized group of patients.

Statistically significant difference was set to $p < 0.05$.

Results

The hospitalized group of patients suffering from oral candidiasis ($n = 30$) included 17 women and 13 men. Chemotherapeutic protocol for treatment of leukemia was assigned for 4 patients, 2 for treatment of lymphoma, 3 for breast

cancer, 6 for malignancies of digestive organs, 3 for prostate cancer and 1 for ovarian cancer. A total of 4 subjects was treated with irradiation therapy for breast cancer, 4 for oral cancer, 2 for thyroid cancer, and 1 for uterine cancer. All patients had pronounced inflammatory changes on the oral mucosa with pseudomembranes. Microbiological analysis proved oral candidiasis in all patients. Average patient age was 61.23 ± 9.07 years (Table 2).

The control group of patients with oral candidiasis ($n = 30$) included 11 males and 19 females. Denture stomatitis was diagnosed in 14 patients, 13 had acute atrophic candidiasis, and 3 patients developed acute pseudomembranous candidiasis. Clinical diagnosis of oral candidiasis was confirmed in all patients through microbiological analysis. Average patient age in this group was similar to the study group (Table 2). The distribution of different species in both groups is presented in table 3. Of 30 isolates, collected from 30 patients, *C. albicans* was detected in 27 (90%), two (7%) isolates

Table 2

Parameter	Patients		p-value
	Hospitalized	Non-hospitalized	
Total number of patients	30	30	
Gender (m/f), n	13/17	11/19	0.60*
Age (years), $\bar{x} \pm SD$	61.2 \pm 9.0	58.7 \pm 11.6	0.05**

m – male; f – female; \bar{x} – mean value; SD – standard deviation.

*Student-*t* test; ** χ^2 test.

Table 3

Candida spp.	Hospitalized patients (n = 30)	Non-hospitalized patients (n = 30)	p-value
	n (%)	n (%)	
<i>Candida albicans</i>	27 (90)	27 (90)	
<i>Candida kefyr</i> *	2 (7)	2 (7)	1**
<i>Candida famata</i> *	1 (3)	1 (3)	
<i>Candida glabrata</i> *	0 (0)	0 (0)	

*Categories pooled for data analysis because of the small number in cells; **Fisher's exact test.

were identified as *Candida kefyr* (*C. kefyr*), and one (3%) as *Candida famata* (*C. famata*). When analyzing 30 isolates collected from non-hospitalized patients, the main isolate was *C. albicans* in 27 (90%) cases, in two (7%) samples *C. kefyr*, and in one (3%) *C. glabrata*.

Discussion

Fungal infections pose a significant source of complications in patients suffering from malignancies. During the last 50 years their numbers increased, they frequently develop in early stages of the disease, and are caused by the species which had not been previously considered as pathogenic¹⁴⁻¹⁶. Cytotoxic and radiation therapies are important predisposing factors in the development of oral candidiasis. While the organism had already been weakened by the principal disease, its defense mechanisms are further depleted by those treatment modalities^{6,17}. In addition, a consequence of these therapies is frequently oral mucositis, which is mainly caused by their direct cytotoxic effect on mucosal cells as well as a negative effect of long-standing inflammation due to inadequate immune reaction to fungal infection¹⁸. It is estimated that 30–70% of the patients on cytotoxic therapy develop oral candidiasis. Moreover, negative side-effects of radiation therapy in the head and neck regions, such as dry mouth and thick sticky saliva, are coupled with an increase in colonization with *Candida* spp, especially *C. albicans*. Such a milieu favors the development of oral candidiasis in 17% to 52.5% of the patients^{8,19-21}. In all our test subjects, clinical examination and microbiological analysis proved oral candidiasis.

Most superficial fungal infections of the oropharyngeal region and digestive system are caused by *C. albicans*²². In immunologically challenged patients, this fungus may cause an invasive infection through damage and ulcerations of the mucosal surfaces. Disseminated type of the infection may appear in cases of neutropenia, hematologic malignancies, and in patients on high dose-regimens of antimicrobial and cytotoxic therapy^{23,24}. In this research, *C. albicans* was the

most common cause of the infection, and these results correspond to the majority of other investigations. Nicolatuo-Galitis et al.¹⁹ investigated patients in irradiation therapy; a total of 61 patients participated, and pseudomembranous candidiasis developed in 31 patients. The most commonly isolated fungus was *C. albicans* (84%), followed by *C. tropicalis* (9%), *C. glabrata* (3.4%), *Candida krusei* (1.2%) and *Candida holmii* (1.2%). Similar results were obtained by Swoboda-Kopec et al.²⁵. The main causative agent was *C. albicans*, while of non-*albicans* *Candida* significant role in infection was played by *C. glabrata*, *C. krusei*, *C. tropicalis*, *C. parapsilosis* and *C. kefyr*. The cases where *C. albicans* is isolated as the main causative agent range from 51–93%^{25,26}. These results are in line with our results since in our patients 90% of the infections were caused by *C. albicans*.

To a lesser extent (6%) we were able to isolate *C. kefyr* in our patients. It is well known that *C. kefyr* may cause superficial infections. Besides, some cases of fungaemia caused by this fungus have been described in hospitalized patients both from departments of surgery and oncology²⁷. *C. famata* is a saprophyte which rarely causes infections in humans, however, there are case reports of fungaemia and peritonitis in hospitalized patients. In addition, it may cause urogenital infections and deep fungal infections of heart or lung tissue with the subsequent development of sepsis. In our investigation, one of the subjects was positive on *C. famata* infection²⁸.

C. glabrata had been considered as a harmless member of the oral flora; however, it has recently been identified as a significant causative agent of infections in immunologically compromised patients. In patients submitted to irradiation therapy, *C. glabrata* is regarded as an important cause of oropharyngeal candidiasis. The probability of *C. glabrata*-caused infection of the oral mucosa is significantly increased if the previous fungal infection was treated with fluconazole or ketoconazole^{29,30}. In hospitalized patients who participated in this research, no *C. glabrata* isolate has been detected, but we have isolated this fungus from the one of the control patients' oral mucosa.

Conclusion

This study confirmed that oral candidiasis in patients with malignant diseases treated with irradiation and chemotherapy is

mostly caused by *C. albicans*. It is to be expected that *C. albicans* will remain the most significant causative agent of oral candidiasis, although other species should also be taken into account (such as *C. kefyr* and *C. famata*).

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