

Evaluation of distribution of different species of *Candida* in cancer patients

Khatereh Kheirollahi¹, Seyyed Hossein Hekmati Moghadam², Gooya Kabir³, Zaleh Zare Mehrjardi^{4*}

1- Department of Oral Medicine, School of Dentistry, Shahid Sadoughi University of Medical Sciences, Yazd, Iran.

2- Department of Pathology, Shahid Sadoughi University of medical Sciences, Yazd, Iran.

3- Department of Oral and maxillofacial surgery, Shahid Sadoughi University of Medical Science, Yazd, Iran.

4- Department of Dentistry, Shahid Sadoughi University of Medical Science, Yazd, Iran.

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*Correspondence:

Zaleh Zare Mehrjardi

Department of Dentistry, Shahid Sadoughi University of Medical Science, Yazd, Iran

khaterekheirollahi@yahoo.com



Abstract

Background and objectives: Patients undergoing chemotherapy are severely susceptible to infections due to a compromised immune system and also their oral cavity is a great place for microorganisms and fungi to grow. The aim of this study was to determine the distribution of different strains of *Candida* from oral lesions of these patients.

Methods: This descriptive study was performed on 128 patients undergoing chemotherapy in teaching hospitals of Yazd, which was three weeks passing receiving their first medicine. Oral samples were prepared from swabs and then cultured in Sabouraud dextrose agar culture media for evaluation of yeast growth, colonization, and identification of species. Samples were examined under the microscope and recorded. Finally, the data were analyzed by SPSS17 software, Chi-square, and Man-Whitney tests.

Results: 128 patients participated in this study, which included 45 males (35.15%) and 83 females (64.85%) with an average age of 40.16 ± 19.95 years. 84 patients (62.65%) had candida in their oral cavity, of which 79 were candida albicans and 5 were Non-albicans *Candida*. No significant correlation was found between the type of candidates, type of cancer and the frequency of *Candida albicans* with the age and sex of the patients (P -value <0.05).

Conclusion: Based on the results of this study, the prevalence of *Candida albicans* in patients undergoing chemotherapy is higher than Non-albicans *Candida*. Patients with leukemia are more susceptible to *Candida* infections.

Keywords: Oral Candidiasis, Chemotherapy, Cancer



Introduction

Cancer is one of the growing diseases in the world today, which is causing many deaths around the world every year (1), according to WHO (2009), the number of people with cancer will reach 15.5 million in 2030 from 11.3 million people in 2007 globally, and during that same period, deaths will grow from 7.9 million to 11.5 million people (2).

Currently, existing therapies for cancer include surgery, radiation therapy, and chemotherapy. Surgical and radiation therapies could be effective if the tumor is limited and other organs are not involved; otherwise, a systemic intervention, such as chemotherapy, will be needed to treat cancer effectively, which is only useful in about 10 to 15% of cases (1, 3, 4).

Cancer treatment by chemotherapy drugs to eliminate cancer cells usually associated with unwanted side effects that can endanger the patient's health and quality of his life, despite its significant role in the treatment of malignancies. Oral problems such as mucus-oral inflammation, dry mouth, and various infections are common complications in these patients (4-6).

Patients on chemotherapy are highly vulnerable to infections due to the compromised immune system, and oral cavity is a greatly suitable place for the growth of microorganisms and fungi which causing death in these patients (7, 8). Observed in patients on chemotherapy that the normal oral flora including streptococci and diphtheria are decreasing, while Gram-negative bacillus species such as *Escherichia coli*, *Klebsiella* and *Pseudomonas* are significantly increasing. The rise

of *Candida* species and Candidiasis are also commonly found following chemotherapy (9).

Fungal infections cause many problems, such as pain, burning and eating interactions during treatment for the patient (8, 10). There are various species of fungi in the mouth and throat, such as *Aspergillus*, *Candida*, etc., that can cause systemic mucositis following fungemia, and its prevalence has increased in Europe over the last ten years, which can be accompanied by an increasing morbidity and mortality rate (11).

Candida species colonize all human mucosal surfaces shortly after birth, and the risk of endogenous infections with these agents is always present. Candidiasis is the most common systemic mycosis which its most common type is *Candida albicans* (12, 13).

For instance, in the study done by Gentle *et al.* in 2003 in England, the colonized *Candida* was found to be 25% in the ALL children group and 7.5% in the healthy group (14). Also, a study by Maheronnaghsh *et al.* in 2014 in Isfahan showed from 385 cancer patients underwent chemotherapy, 55 (14.3%) of them had *Candida* which 26 were *Candida albicans* and 10 were non-*albicans Candida* (15). Considering the above-mentioned issues, the study of candidates for *albicans* and non-*albicans* in patients on chemotherapy due to the high prevalence of these infections seems necessary. Therefore, the present study was conducted to evaluate the frequency distribution of different strains of *Candida* in patients on chemotherapy.

Materials and Methods

This observational study was conducted in a one-year interval on 128 undergoing chemotherapy that stay in the Yazd teaching hospitals and 3 weeks were passed from receiving the first dose of their chemotherapy (11).

Patients are excluded from the study by taking any antibiotic, mouthwash and any treatment outside standard regimen, immune deficiency and diabetes mellitus, smoking, or other condition that cause candidacies (e.g. Dry mouth, using removable prosthesis)(15). A questionnaire form was developed to record the medical history of patients, type of cancers, and demographic data. This research has been approved by Shahid Sadoughi University of Medical Sciences/Ethics Committee (IR.SSU.REC.1396.123). Then the purpose of the study was explained to patients and conscientious written consent was obtained.

Sampling was carried out by two wet swabs transferring in tubes containing 0.5 ml of saline solution (16). Then each swab was placed in a disposable plastic tube containing 1 ml of normal saline and inserted in an incubator at 37 ° C and transferred to the laboratory within a maximum of 2 hours for running microbial culture.

In the laboratory, the swabs were cultured on a cultivating environment of Subouraud's dextrose agar, Subouraud's Cycloheximide Dextrose Agar and Subouraud's Cycloheximide Chloramphenicol Dextrose Agar (commercially available from Mardavash Iran Co.). The cultivating environments were kept at 37 ° C for 48 hours and then the candidiasis colonies were removed and Gram staining was performed. The samples were then examined under a microscope and the

results were recorded. To determine the albicans and non albicans of yeast, the germ tube test was performed, in which the colony was incubated in the vicinity of the plasma for 3-4 hours and examined by a microscope, the presence of the germ tubule showed that it was albicans strain (17). The collected data were analyzed using SPSS 17 software, Chi-square and Mann-Whitney tests at a significant level of 0.05.

Results

Among 128 patients with various type of cancer who undergoing chemotherapy in Yazd teaching hospitals. Of these, 45 (35.15%) were male and 83 (64.85%) were female. The mean age of the patients was 40.16 ± 19.95 years with a range of 1 to 86 years.

The results of this study showed that 84 patients (65.62%) had candida in their oral cavity. The causative agents of oral candidiasis in cancer patients undergoing chemotherapy were *C. albicans* 79 and non-albicans 5.

As mentioned in Table 1, candidiasis in the oral cavity was seen in 66.3% of women and 64.4% of men, as well as 72% of subjects under 18 and 64.1% of those over 18 years of age. Chi-square test showed no statistically significant correlation between the frequency of *Candida* with age (P-value = 0.493) and gender (P-value = 0.308).

In Table 2, the relative frequency of Albicans and Non- albicans candidates in the patients is presented. As seen, from all of the candidate samples observed in the oral cavity of patients, 96.4% of women and 89.7% of men and 88.9% of patients under the age of 18 and 95.5% of patients over 18 years of age were having candida albicans, and the rest of the cases consisted of non- albicans *Candida*. Chi-square test showed no significant correlation between

the type of candidate with age (P-value = 0.222) and sex (P-value = 0.290).

Table 1 : Frequency of Candida in studied patients in terms of demographic variables

Demographic variable \ Candida		Yes		No		p-value
		count	%	count	%	
sex	woman	55	66.3	28	33.7	0.493
	Man	29	64.4	16	35.6	
age	<18	18	72	7	28	0.308
	>18	66	64.1	37	35.9	

Table 2: The relative frequency of Candida albicans and non-albicans Candida in the studied patients in terms of demographic variables

Demographic variable \ Candida type		albicans		Non-albicans		p-value
		count	%	count	%	
Sex	woman	53	96.4	2	3.6	0.222
	Man	26	89.7	3	10.3	
Age	<18	16	88.9	2	11.1	0.290
	>18	63	95.5	3	4.5	

According to the results of the Maan-Whitney test, there was no significant difference between men and women (P-value =0.867), and also between the two age groups (P-value =0.224), in having candida albicans.

The mean and standard deviation of the candidate colony count in the examined patients by gender and age groups studied is presented. The mean number of colonies in men (143.85 ± 274.96) was more than women (121.11 ± 23.65) and in the age group <18 years ($> 168 \pm 294.7$) more than those older than 18 years ($49 / 228 \pm 59/118$).

The results showed that 67.9% of patients with leukemia and 77.3% of patients with other types of cancer had candida in their oral cavity, and in rest

of the cases no candida was detected, but according to Chi-square test, this difference was not statistically significant (P-value = 0.483) (Table 3).

According to the results of study, the Candida albicans was detected in the oral cavity of 22.8% of the patients, who were affected by 77.2% hematologic cancer and 93.8% of the patients with other types of cancer, while only one patient (20%) had hematologic cancer and 4 Patients (80%) were diagnosed with non- albicans Candida, which according to the Chi-square test, this difference was not statistically significant between the group of leukemia and other cancers (0.684= P-value)(Table 4).

Table 3: The relative frequency of Candida in the studied patients according to the type of cancer

Candida \ Cancer type	Hematologic cancer		solid Cancers		Total	
	Count	%	Count	%	Count	%
yes	19	67.9	65	77.3	84	65.6
no	9	32.1	35	79.54	44	34.4

Table 4: The relative frequency of Candida albicans and Candida non-albicans in studied patients according to the cancer type

Candida type \ Cancer type	Hematologic cancer		Solid Cancers		Total	
	Count	%	Count	%	Count	%
albicans	18	94.7	61	93.8	79	94
non- albicans	1	5.3	4	6.2	5	6

The mean and standard deviation of *Candida* colony count in the patients according to the cancer type showed that the number of colonies in patients with leukemia (227.23 ± 363.33) was higher than those with other cancers (99.49 ± 199.59).

Discussion

Candida infections are a major problem for immune compromised patients in worldwide, especially in those on chemotherapy(18), and in these patients, the main cause of opportunistic microbial infection is fungal species belonging to the candida species (19, 20). Various species of *Candida*, including *Candida albicans*, is a part of the normal microorganism flora of the human body that exists in the cutaneous and mucous surfaces, skin, oral, digestive system and human vagina. The cause of 90% of invasive and relatively common Candidiasis is non-*albicans* such as *C. glabrata*, *C. tropicalis*, *C. parapsilosis* and *C. krusei* (15) Obviously, with the weakening of the immune system, this flora is usually pathologically induced and candidiasis is caused (21, 22).

The present study aimed to determine the frequency distribution of different isolates of *Candida* in patients undergoing chemotherapy. Samples were taken by sterile swab in oral cavity. Swab at the site of the lesion is a relatively simple method for diagnosis of growth and candida estimation. In general, when a lesion is available and visible, direct sampling methods such as swabs was preferred (21), also due to weakness, anxiety and lack of shuffling in chemotherapy patients convincing them to use swabs It was easier to sample than asking them to collect saliva. Although *Candida* species grow well in most culture environments, the preferred environment for Subouraud's dextrose agar contains

antibacterial (23), also cheaper than colorants(24).

The frequency distribution of different *Candida* strains from oral samples in chemotherapy patients in the present study showed that 84 patients (65.62%) had candidosis in their oral cavity. *Candida albicans* are ranked as the most common cause of candida around the world(25, 26). This trend has been observed over the last decade, even in developed countries such as the United States, Denmark, Norway and Finland (27). In similar studies, the prevalence of *Candida albicans* has been reported more than other types of candida; For example, Davies et al. Observed the prevalence of oral fungi among 120 advanced cancer patients and showed that the *Candida albicans* (46%), *glabrata. C* (18%), *Candida C. dubliniensis* (5%) and other species (5%) were the most frequent respectively (28). In a study by Jain et al., 70% of 50 cancer patients underwent chemotherapy had candida in their oral cavity. In the Humada study, out of 102 cancer patients, 46 cases of *Candida* infection were strained; which 63.3% of them were *Candida albicans* and 36.7% were non-*albicans* candida (*C. parapsilosis* (7%), *C. tropicalis* (8.4%), *C. glabrata* (6%) and *C. krusei* (5%))(29). In the present study, 84 cases were diagnosed as candida, 79 cases were *Candida albicans*, and only 5 cases were non-*albicans* *Candida*. In a study by Maheronnaghsh et al. In Isfahan, of 385 chemotherapy-induced cancer patients, 55 (14.3%) had candida, of which 26 were *Candida albicans* and 10 were *Candida non- albicans* (15), while In our study, from 128 patients, 84 patients (65.62%) had candida in the oral cavity, of which 79 cases were *Candida albicans* and 5 cases of *Candida non- albicans*. The inconsistency of this study's results with the results of the study by Maheronnaghsh et al (15) can be due to the fact

that oral antifungal mouthwash is probably used in Isfahan to prevent oral complications of chemotherapy, or oral hygiene is regularly monitored.

Candida colonization and as a result of invasive candidiasis in patients with opportunistic infections are more likely than those who are healthy (24). The results of the Humada study in oral cancer culture in 102 cancer patients in Tikrit's educational hospital in the city of Tikrit showed that in 45% of patients, the result was positive culture, the incidence of oral candidiasis increased with age, and in Women (67.3%) were more likely than men (32.7%) (29). In the present study, although there was no significant difference, *Candida albicans* were observed in female oral specimens (96.4%) more than men (89.7%) and increased with an increase in age (9.9% 88% of patients under the age of 18 and 95.5% of patients over the age of 18), which is consistent with the results of the Humada study (29).

Immune system inhibitors such as chemotherapy in cancer patients cause invading candidates (30). As invasive candidiasis is one of the most common and potentially lethal side effects of cancer and chemotherapy associated with it (31, 32). On the other hand, some types of cancer may require more chemotherapy drugs than other cancers (such as hematological cancers), which is called invasive chemotherapy. The aggressive chemotherapy weakens the patient's immune system and can put the patient at risk for a fungal infection (33).

The prevalence of *Candida albicans* and other fungi in patients is quite different according to the type of cancer (19). Davies et al. in their concluded that confirm a shift in the species of yeast isolated from the oral cavities of patients

with advanced cancer, with an increase in the isolation of non-*C. albicans* species(28), but the results of Pagano et al. and Maheronaghshet al. Studies also showed that people with leukemia or myeloma may have a higher risk of developing fungal infections than those with other cancers (15, 34). Based on the results of the current study relation between cancer types group and candidiasis in patients undergoing chemotherapy, were 65% as a Solid tumor group and 67.9% as a hematological group, the presence of *Candida albicans* was detected in the oral cavity of 22.8% of the patients in hematological group and 77.2 % of the patients involved in other types of cancer, whereas only one patient (5.3%) had hematological group And 4 (62.2%) patients with other types of cancers were diagnosed with non- *albicans Candida*. The results of the current study confirm a shift in the species of yeast isolated from the oral cavities of patients with advanced cancer, with an increase in the isolation of non-*C. albicans* species. The main explanation for this phenomenon is the increased use of antifungal drugs.

Patients' lack of cooperation due to their psychological discomfort which was reduced by justifying the sampling procedure was one of the problems of the present study.

Conclusion

The findings of this study showed that the prevalence of *Candida albicans* in the mouth of patients undergoing chemotherapy was higher than non- *albicans Candida*. Women are more susceptible to *Candida* infection than menslightly but not significantly, like young adults than adults. Also, the presence of *Candida albicans* was more commonly diagnosed in the oral cavity of patients with leukemia than other types of cancer.

According to the results of the study, it is suggested that the dentist's participation should start before the beginning of cancer treatment in order to promote the health status of cancer patients under chemotherapy, and there should be interaction between the doctor and the dentist throughout the treatment process and also necessary prevention information. And treatment of oral complications, especially for candida infection should be given to the patients.

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Conflict of interest:

The authors declare that there is no conflict of interest.

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