

Oral Candidiasis in Leukemia Patients

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ABSTRACT

Background: Oral *candidiasis* are mycoses resulting from the overgrowth of yeasts of the *Candida* genus, represents a serious problem for patients with leukemia. The mortality rate of this infection has increased due to fungal septicemia, associated with a primary buccal infection.

Objective: The aim of our study is to determine the prevalence of oral *candidiasis* in leukemia patients, identify the *Candida* spp. in buccal lesions, differentiate the factors that influence their development.

Patients and methods: This is a retrospective and descriptive study conducted over a four-months period from November 7, 2016 to March 2, 2017, including patients diagnosed with leukemia. Sociodemographic, clinical and biological data from patients fulfilling the inclusion criteria were collected and analyzed.

The lesion sample was taken and studied by direct exam and culture on Sabouraud Chloramphenicol and Sabouraud Chloramphenicol Actidionne. The identification of the isolated yeast was done by the filamentation test, carbohydrate fermentation and assimilation.

Results: 56 patients were included in this study. Most of the cases (48,21%) were positive to oral *candidiasis*. Their average age was 33,86 years, they were mainly made up of men (64,28%).

Candida albicans was the most frequent species found (55,55%), followed by *Candida glabrata* (22,22%), *Candida tropicalis* (14,81%) and *Candida krusei* (7,40%). The main contributing factor found was parenteral nutrition (55,55%), corticosteroid therapy (55,55%), antibiotherapy (37,03%), neutropenia (25,92%) and diabetes (11,11%).

Conclusion: The results suggest that oral *candidiasis* is a frequent complication in the leukemia patients. *C. albicans* was the main etiological agent, however, there is an important participation of other *Candida* species.

Keywords: Oral *candidiasis*; Leukemia patients; *Candida* spp

INTRODUCTION

Oral *candidiasis* is extremely common. It is a yeast infection of the oral mucosa caused by a fungus of the genus *Candida*. Today there are more than 200 species belonging to the genus *Candida*, 23 of which are pathogenic for humans, *Candida albicans* is responsible for infection which, by their frequency and severity, rank first among fungal infections. Others *Candida* species are occasionally pathogenic for the oral cavity: *Candida tropicalis*, *Candida pseudotropicalis*, *Candida glabrata*, *Candida guilliermondii*, *Candida krusei*, *Candida parapsilosis* [1]. These yeasts are part of the normal flora of most individuals and live as commensals in the oral mucosa, the digestive tract, the urogenital tract and the skin covering, becoming opportunistic when local conditions become favorable for its growth [1,2]. The transition to pathogenicity is linked to

several factors including broad-spectrum, antibiotic therapy, immunosuppression, neutropenia, chemotherapy, hematologic malignancies, cancers, diabetes and acquired immunosuppression (HIV) [3].

Oral *candidiasis* is often encountered in immunocompromised patients, leukemia patients being an example. Diagnosis is generally easy, based on clinical and laboratory criteria [4]. The mycological diagnosis of *candidiasis* is part of the approach based on clinical and biological criteria and the classic identification of a microorganism. Direct examination of the surface sample is followed by cultivation to isolate the germs in question. The isolated yeast colonies can then be identified by carrying out various tests which are based on morphological, immunological, biochemical and even genotypic criteria [5,6].

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PATIENTS AND METHODS

This is a cross-sectional descriptive observational study, carried out over a period of four months from November 7, 2016 to March 2, 2017 in collaboration between the laboratory of Parasitology and Medical mycology and the hematology service at the Hospital Center University (HCU) and the Anti-Cancer Center (ACC) of Batna-Algeria.

All leukemia patients of both sexes were included in our study. Professional secrecy has been safeguarded and the patient's consent requested and obtained in advance. Patients recently diagnosed with leukemia and not yet treated with chemotherapy or corticosteroid therapy favoring the onset of oral *candidiasis* were excluded from our study. This study is based on an information sheet which contains information on the patients, specifying age, sex, reason for hospitalization and risk factors.

We performed a total of 56 oral swabs. These were carried out by swabbing the diaper using sterile cotton swabs on the internal face of the cheeks, the soft palate, or an acute lesion. They are sent to the parasitology and medical mycology laboratory for direct examination and cultivation on Sabouraud-Chloramphenicol and Sabouraud-Chloramphenicol.

Actidionne medium, incubated at 37°C for 24 to 48 hours. The *Candida* colonies that have appeared measure a few millimeters in diameter. Rather whitish, their surface is smooth and shiny. The microscopic examination is carried out on a colony resulting from the culture, it is examined between slide and coverslip by adding a drop of KOH or cotton blue, it allows the detection of yeasts in spherical or ovoid form measure of 4-5 µm with or without bud.

The identification of the isolated yeast was done by the filamentation test, carbohydrate fermentation and assimilation.

RESULTS

Distribution of cases of diagnosed oral *candidiasis*

Out of 56 patients included in our study, 27/56 (48,21%) had proven oral *candidiasis* (Figure 1).

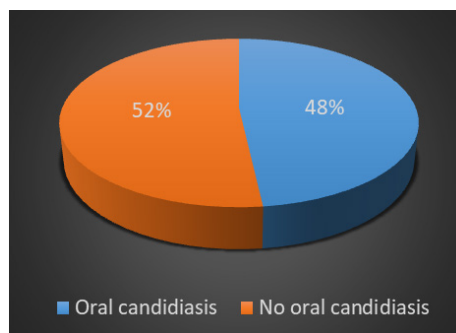


Figure 1: Distribution of cases of diagnosed oral candidiasis.

The male sex was the most representative with 36/56 (64.28%), with a sex ratio of 1.8 (Figure 2).

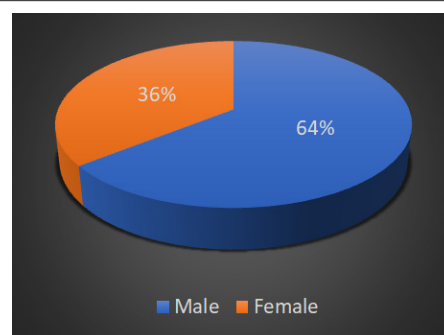


Figure 2: Distribution of patients by sexes.

The average age was 35.86 years old. The most representative age groups are in the 15 to 30 year range (Figure 3). The mean age of the patients is 35.86 years; the median is 38 years with ranges of [6-75 years].

Services

The hematology service of the University Hospital Center was the most representative of the positive results with a number of 17 cases (54.84%), followed by the hematology service of the Anti-Cancer Center with 7 cases (36.84%), which is also followed by the day hospital with 3 cases (50%) (Table 1).

Table 1: Breakdown of all results at the service level.

Service	Résult+		Résult-		Total	Percentage
	Effective	Percentage	Effective	Percentage		
Hématology UHC	17	54,84%	14	45,16%	31	55,36%
Hématology ACC	7	36,84%	12	63,16%	19	33,93%
Day hospital	3	50%	3	50%	6	33,93%
Total	27	100%	29	100%	56	100%
343	343	343	343	343	343	343

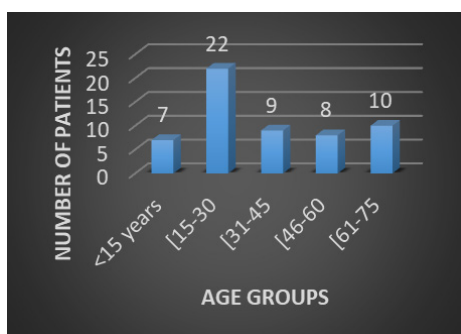


Figure 3: Distribution of patients by age groups.

Mycological data

Of the 27 positive cultures, *Candida albicans* was isolated in 15 cases (Figures 4 and 5).

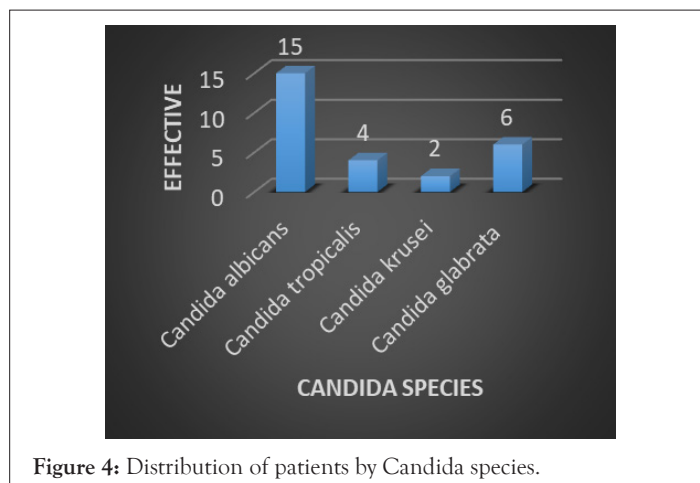


Figure 4: Distribution of patients by *Candida* species.

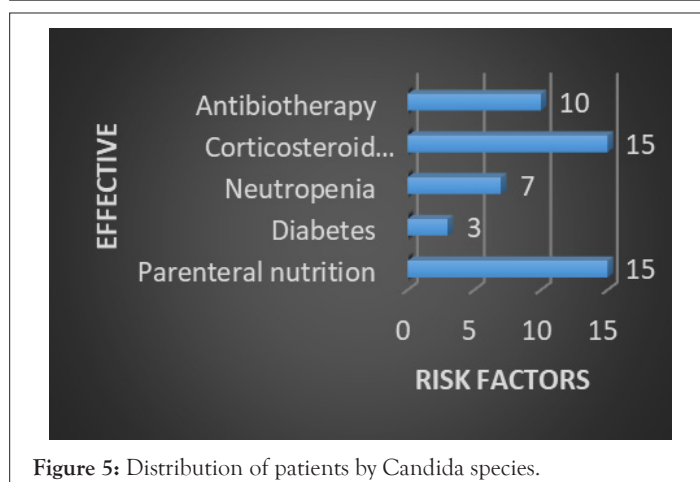


Figure 5: Distribution of patients by *Candida* species.

The main contributing factor found was parenteral nutrition 15/27 (55,55%), corticosteroid therapy 15/27 (55,55%), antibiotherapy 10/27 (37,03%), neutropenia 7/27 (25,92%) and diabetes 3/27 (11,11%).

DISCUSSION

Oral *candidiasis* is a big problem for people with leukemia because of the possibility of a potentially fatal systemic infection. *C. Albicans* is the main causative agent, but there is significant involvement of other species. The *Candida* species existing in the mouth have a high probability of infecting the digestive tract and spreading through the circulation, developing a systemic infection which threatens the life of the sick.

Our objective in this study was to determine the prevalence of oral *candidiasis* in leukemia patients, to identify the *Candida* species involved and to assess the risk factors.

In our study, the prevalence of oral *candidiasis* was 48.21%, this result is far from that reported by Yahyaoui [7] in the MOHAMMED V RABAT military training hospital in 2013, which found a percentage of 81.8%. Another study by Gravina et al, in Maracaibo (Venezuela), reported a rate of 69.35% [8]. The 16-30 age group was the most representative with 39.29% of cases, a result close to that found by Dembel MA during an epidemiological clinical study on oral *candidiasis* at the National Center of Odonto Stomatology (CNOS) of Bamako in 2007 which showed that the age group of

20-29 is the most representative with a percentage of 27.4% [9].

Leukemia is a malignant proliferation of hematopoietic tissue, there are four types of leukemia: Acute Lymphoblastic Leukemia (ALL), Chronic Lymphocytic Leukemia (CLL), Acute Myelogenous Leukemia (AML), Chronic Myeloid Leukemia (CML), and Acute Lymphoblastic Leukemia (ALL) especially those aged 16 to 30 years (70%). Previous studies have shown that acute lymphoblastic leukemia mainly affects children but also adults to a lesser extent, it is favored by several risk factors: Genetic, toxic chemicals, physical, as well as anticancer treatments received previously [10].

In our studies, the male sex was the most represented (64.29%); the sex ratio was 1.8 this can be explained by the fact that leukemia affects men much more than women. Epidemiological data in France in 2012 indicate that the crude incidence rate of Acute Lymphoid Leukemia (ALL) is 1.6/100,000/year in men and 1/100,000/year in women and that of Acute Myeloid Leukemia (AML) is 2.8/100,000/year in men and 2.5/100,000/year in women [10].

We found 27 positive cultures, *Candida albicans* was demonstrated in 15 cultures (55.56%), a result similar to several studies [7,8]. These results can be explained by several parameters, related either to the host or to the species itself. *Candida albicans* is a saprophyte of the oral cavity, it becomes pathogenic under the influence of changing environmental conditions in its host [11]. The results obtained further prove the performance and superiority of *Candida albicans* caused infection over all other *Candida* species; this capacity is linked to the various virulence factors which characterize it. These factors include polymorphism, adhesion and biofilm formation [12]. Importantly, most epidemiological studies have pointed to the emergence of non-*albicans* species over the past two decades [13]. Oral *candidiasis* are serious opportunistic infections in immunocompromised patients. They represent a frequent complication in onco-hematology. The change to the pathogenicity of *Candida* is linked to several factors including cytotoxic treatment, neutropenia, broad-spectrum antibiotic therapy, immunosuppression secondary to corticosteroid therapy and diabetes [14]. According to our result 25.93% of the patients were neutropenic. This rate is close to that found by Stinnent et al 1992 (30.95%) [14].

Malignant disease also promotes oral *candidiasis* through the immunosuppression caused by chemotherapy. Most chemotherapy drugs can induce neutropenia 8 to 16 days after administration. Leukemia is accompanied by febrile neutropenia characterized by fever ($\geq 38.3^{\circ}\text{C}$) and a decrease in the number of circulating neutrophils. Polynuclear neutrophils constitute the first line of defense of the mucous membranes against *Candida*. They have a crucial role in the initiation of cellular and humoral immunity. They secrete soluble mediators such as IL-1, IL-6 or TNF- α . PNNs have many properties including:

*Limitation of tissue colonization.

*Protection against the dissemination of endogenous yeasts.

*Zn²⁺ dependent fungistatic activity characteristic of PNNs by blocking *Candida* filamentation.

*Modification of the composition of the fungal cell during the *Candida*-PNN interaction.

*Release by dead PNNs of a protein inhibiting the growth of *Candida*.

The intensity and duration of neutropenia are risk factors for infection in leukemic patients [15].

Exposure to broad-spectrum antibiotics is another key risk factor for oral thrush, 37.04% of our patients were treated with broad-spectrum antibiotics. Likewise Pauld, found that 42.1% of patients with oral *candidiasis* were put on broad-spectrum antibiotic therapy [16]. Another study carried out at the level of the geriatric ward reported that 95% of patients with oral *candidiasis* had previously been exposed to antibiotics [17]. The use of antibiotics can contribute to the development of fungal infections by changing the ecology of the resident microflora, opportunistic microbes like *Candida* can take advantage and grow rapidly in the surfaces of the mucous membranes, when the integrity of these the latter is ruptured, a locally invasive infection develops and secondary hematogenous dissemination can then ensue, even with a decrease in immunity. The duration of treatment can also have an impact, the longer it is, the greater the risk [18].

Corticosteroid therapy: During our work we found that 55.56% of *candidiasis* patients were on corticosteroid therapy. The Stinnett E study in leukemic children for oral *candidiasis* research reported a rate of 21.1% of the population were on corticosteroids [14].

Inhaled or systemic corticosteroids have a major impact on the occurrence of oral *candidiasis*. They interfere with macrophage and neutrophilic functions. The risk of fungal infection increases with the dose and duration of corticosteroid therapy. In autoimmune diseases, the dysfunction of the T cell response necessary to stimulate granulocytes increases the risk of infection [19].

Diabetes is a very common disease which has become one of the greatest public health burdens due to its degenerative complications. Oral *candidiasis* in diabetic patients is also common. As part of our study, we evaluated the prevalence of oral *candidiasis* in this field where three cases were reported (11.11%). This prevalence is explained by the availability of the highest levels of sugar in the oral microenvironment, which promotes the adhesion of *Candida* to epithelial cells, which amplifies the development of *Candida* and activates the expression of virulence factors [20]. A prospective study of 150 type 2 diabetic patients has shown that 47% of patients have oral *candidiasis* [21,22].

CONCLUSION

Our study made it possible to underline the interest which should be shown in onychomycosis in terms of their frequency and to better understand the epidemiological, clinical and mycological characteristics of onychomycosis. This study reinforces the importance of mycologic confirmation of onychomycosis in any patient with onychopathy, allowing treatment to be adjusted and long, costly and ineffective treatment to be avoided.

COMPETING INTEREST

The authors declare that they have no conflict of interest directly or indirectly related to this article.

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