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INVESTIGATION OF THE PREVALENCE OF CANDIDURIA IN PATIENTS WITH HEMATOLOGIC MALIGNANCIES IN HOMS – SYRIA

Rafah Alali[1*], Walid Khaddam[1] and Sundus Yaseen[2]

[1]*Department of Biochemistry and Microbiology, Faculty of Pharmacy, Al-Baath University, Homs, Syria*
[2]*Department of Biochemistry and Microbiology, Faculty of Pharmacy, Al-Kalamoon University, Deratiah, Syria*

The aim of this study was to investigate the incidence of candiduria in patients with hematologic malignancies, and identity its causative agents. The study included 100 patients with one of the following diseases: Acute myeloid leukemia (AML), Chronic myeloid leukemia (CML), Acute lymphoid leukemia (ALL), Chronic lymphoid leukemia (CLL), Multiple myeloma (MM), Hodgkin's lymphoma (HL) and Non-Hodgkin's lymphoma (NHL), who were admitted to the Hematology Department in some hospitals in Homs-Syria between December 2020 to September 2021. Candida species were identified by colony color on CHROMagar candida, germ tube production and micro-morphology on cornmeal agar. Among the 100 patients, 13 (13%) were positive for candiduria. C. albicans was the most common cause of candiduria (61.5%), followed by C. tropicalis and C. krusei (15.4%, respectively) and C. dubliniensis (7.7%). According to the results of the statistical analysis, candiduria was found to correlate significantly with female gender, previous exposure to a urinary catheter, acute myeloid leukemia (AML) and severe neutropenia (<500 cells/mm^3).

***Keywords**: Candiduria, Fungal infections, Hematologic malignancies, Opportunistic infections.*

INTRODUCTION

Fungal diseases kill more than 1.5 million and affect over one billion people annually. However, they are still a neglected topic by health professionals[1-2]. The prevalence of opportunistic fungal infections has increased in the past few decades[3-5]. Opportunistic fungal infection is one of the most prevalent causes of mortality and morbidity in immunocompromised patients [6]. Patients with hematologic malignancies receive cytotoxic chemotherapy. Consequently, they are severely immunosuppressed patients[4-9]. Chemotherapy affects the rapidly dividing cells, this leads to epithelial barrier disruptions that facilitate invasion by microorganisms. In addition, chemotherapeutic agents reduce the number of neutrophils that defend the host against organisms[10]. *Candida* species are considered important parts of microbial normal flora in the oropharyngeal cavity, gastrointestinal tract and vagina in the healthy people[11]. Immune deficiencies may lead to disturbances in candida's normal homeostasis, resulting in a transition from normal flora to opportunistic pathogenic microorganisms causing infection of the urinary tract with *candida*[12]. The term candiduria is used to describe the presence of *candida* spp such as *C. albicans* in the urine[13]. *Candida albicans* is the most common causative agent (50%- 65%) of candiduria[14]. Candiduria is diagnosed through colony counting where 10^3 CFU/ml urine is the minimum considered by the National Institutes of Health[15]. In this study, we investigated the

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*Corresponding author: Rafah Alali, E-mail: rafahali93@gmail.com

prevalence of candiduria in patients with hematologic malignancies and identified the *candida* species isolated.

MATERIALS AND METHODS

Study population

This cross-sectional, descriptive study was conducted on 100 patients with one of the following diseases: Acute myeloid leukemia (AML), Acute lymphoid leukemia (ALL), Chronic myeloid leukemia (CML), Chronic lymphoid leukemia (CLL), Multiple myeloma (MM), Hodgkin's lymphoma (HL) and Non-Hodgkin's lymphoma (NHL), who were admitted to the Hematology Department in some hospitals in Homs-Syria, males and females, with ages ranging from 9 to 85 years, in the period from December 2020 to September 2021. In this study we excluded:

1. Patients with diabetes
2. Intensive care unit (ICU) patients
3. Renal dysfunction patients
4. Patients treated with antifungal drugs

Ethical statement

Demographic data and informed consent were obtained from all the patients and this study was approved by the Ethic Committee of AL-Baath University, Homs, Syria (Number:1451).

Samples collection

Early morning first urine samples were collected in sterilized plastic bottles after instructing patients to wash the external genitalia well with soap and water, then the samples were sent to the laboratory.

Processing samples

The samples were centrifuged at 2000 rpm for 15 minutes, part of the urine sediment was used for direct microscopic examination and the remaining part was cultured on CHROMagar candida medium (CHROMagar candida, France). The culture media were incubated at 35°C for 48 hours aerobically before being considered negative.

Identification of *candida*

Candida isolates were identified based on colony color on CHROMagar candida, germ tube formation and micro-morphology on cornmeal agar including 1% tween 80. Differentiation was made between *Candida* species that gave a positive result in the germ tube test by culturing them on Sabouraud dextrose agar medium (SDA) at a temperature of 45°, in contrast to *candida dubliniensis*, *candida albicans* can develop at this temperature.

Statistical analysis

The results and demographic data were analyzed using Chi-square test in Statistical Package for the Social Sciences (SPSS), version 21. A P-value< 0.05 was considered statistically significant.

RESULTS AND DISCUSSION

Results

The present study included 100 patients with hematologic malignancies, 48 (48%) were males and 52 (52%) were females. The mean age of these patients was 51.17 ± 23.52 years with a range of 9 to 85 years. CML was the most frequent disease (20%), followed by NHL (18%), HL (17%), AML (15%), CLL (15%), MM (8%) and ALL (7%). Among the 100 patients, 11 (11%) had a urinary catheter during the previous month of sample collection in our study. According to neutrophil count, there were 21 patients (21%) with severe neutropenia (<500 cells/mm^3), 33 patients (33%) with moderate neutropenia (500-1000 cells/mm^3) and 46 patients (46%) with neutrophil count (>1000 cells/mm^3).

The Demographic and clinical data of patients with hematologic malignancies have been summarized in Table 1.

Table 1: Demographic and clinical characteristics of patients with hematologic malignancies.

Characteristics	Patients (n=100) No. (%)
Sex	
Male	48 (48%)
Female	52 (52%)
Age (years)	
<15	11 (11%)
15-29	15 (15%)
30-44	11 (11%)
45-59	15 (15%)
60-74	28 (28%)
>74	20 (20%)
Underlying hematological diseases	
AML	15 (15%)
ALL	7 (7%)
CML	20 (20%)
CLL	15 (15%)
MM	8 (8%)
HL	17 (17%)
NHL	18 (18%)
Host factors	
Previous urinary catheterization	11 (11%)
Severe neutropenia (<500 cells/mm^3)	21 (21%)
Moderate neutropenia (500-1000 cells/$mm^{3)}$	33 (33%)
Neutrophil count (>1000 cells/mm^3)	46 (46%)

AML: Acute myeloid leukemia, ALL: Acute lymphoid leukemia, CML: Chronic myeloid leukemia, CLL: Chronic lymphoid leukemia, MM: Multiple myeloma, HL: Hodgkin's lymphoma, NHL: non-Hodgkin's lymphoma (NHL).

Among the 100 studied cases, 13 patients (13%) were positive for candiduria (had colony count $>10^3$ CFU/ml urine). *C. albicans* was the most common cause of candiduria in our study (61.5%), followed by *C. tropicalis and C. krusei (15.4%, respectively)* and *C. dubliniensis* (7.7%) as shown in Table 2.

Table 2: The frequency of *candida* species isolated from urine specimens of patients with hematologic malignancies.

***Candida* species**	**Total**	
	Frequency	**Percentage**
C. albicans	8	61.5%
C. tropicalis	2	15.4%
C. krusei	2	15.4%
C. dubliniensis	1	7.7%

Candiduria was more prevalent in females (21.2%) than in males (4.2%). The age group most commonly affected was (60-74) years old (21.4%), followed by (>74) years old (15%), (45-59) years old (13.3%), (30-44) years old (9.1%), (15-29) years old (6.7%) and (<15) years old (0%). Patients who had a previous urinary catheter were more affected (54.5%) than patients who did not have a previous urinary catheter (7.9%). Candiduria occurrence rates varied according to type of hematological malignancy, AML patients were the most frequently affected (46.7%), followed by MM patients (12.5%), NHL patients (11.1%), CLL patients (6.7%), HL patients (5.9%), CML patients (5%) and ALL patients (0%). The neutrophil count group most commonly affected was (<500 cells/mm^3) (33.3%), followed by (500-1000 cells/mm^3) (12.1%) and (>1000 cells/mm^3) (4.3%) as shown in Table 3.

A significant association was noted between candiduria and female gender, urinary catheter, acute myeloid leukemia (AML) and severe neutropenia (<500 cells/mm^3) ($P<0.05$) as shown in Table3.

Table 3: Distribution of candiduria among patients with hematologic malignancies based on different variables.

Variables	Positive isolation No./Total (Incidence%)	P-value
Sex		0.012
Male	2/48 (4.2%)	
Female	11/52 (21.2%)	
Age (years)		0.527
<15	0/11 (0%)	
15-29	1/15 (6.7%)	
30-44	1/11 (9.1%)	
45-59	2/15 (13.3%)	
60-74	6/28 (21.4%)	
>74	3/20 (15%)	
Previous urinary catheterization		0.000
Patients with a previous urinary catheter	6/11 (54.5%)	
Patients without a previous urinary catheter	7/89 (7.9%)	
Underlying hematological diseases		0.005
AML	7/15 (46.7%)	
ALL	0/7 (0%)	
CML	1/20 (5%)	
CLL	1/15 (6.7%)	
MM	1/8 (12.5%)	
HL	1/17 (5.9%)	
NHL	2/18 (11.1%)	
Neutrophil count		0.005
Severe neutropenia (<500 cells/mm^3)	7/21 (33.3%)	
Moderate neutropenia (500-1000 cells/$mm^{3)}$	4/33 (12.1%)	
Neutrophil count (>1000 cells/mm^3)	2/46 (4.3%)	

Discussion

The prevalence of candiduria among patients with hematologic malignancies was (13%). *C. albicans* was the most frequently isolated element (61.5%) in this study. Whereas *C. glabrata* was the most common pathogen isolated (37%) from patients with hematologic malignancies in *Georgiadou et al* study[16], the reason for the difference between the two studies may be attributed to geographical area and environmental conditions such as temperature and humidity, which play an important role in the spread of these fungus.

Similar to our study, a previous study[16] has found a significant association between candiduria and female gender. This may be due to that *candida* species form important parts of the normal flora of the vagina, as it colonizes on outer side of the urethral opening in healthy females, but in the case of immunodeficiency, they can convert into opportunistic pathogenic microorganisms[17]. In addition, the urethra in women is shorter than it is in men, which facilitates reaching the bladder via ascending route[18].

In our study, like a previous study[19] no relation between patient age and fungal infection was observed in patients with hematologic malignancies.

The percentage of candiduria among patients who had a urinary catheter during the previous month of sample collection was higher than in patients who did not have a previous urinary catheter. In addition, we found a significant association between candiduria and urinary catheter ($P< 0.05$). The reason may be that the catheter can cause infection by introducing microorganisms during the catheterization process or by allowing migration of microorganisms into the bladder along the surface of the catheter from the outer surfaces surrounding the external urethra [20].

In this study, like many others[16&21-23] AML patients were the most frequently diagnosed with fungal infection. This may be due to that AML patients undergo intensive chemotherapy which is considered an important risk factor for immunodeficiency (persistent and severe neutropenia)[24].

In agreement with other studies [21&22], a significant association was noted between severe neutropenia (<500 cells/mm^3) and fungal infection in patients with hematologic malignancies. This can be attributed to the fact that neutrophils play a major role in the host response against *candida* infections. In addition, they are the most effective *candida* killers and are the only host cells capable of inhibiting the germination of *candida* into hyphae [25-27].

Conclusion

Candiduria is a common infection in patients with hematologic malignancies, and *Candida albicans* is the most isolated of the *Candida* species. Female gender, previous exposure to a urinary catheter, acute myeloid leukemia (AML) and severe neutropenia (<500 cells/mm^3) are risk factors for candiduria in patients with hematologic malignancies.

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تحري انتشار بيلة المبيضات عند مرضى الخباثات الدموية في حمص – سورية رفاه

رفاه العلي[1]* – وليد خدام[1] – سندس ياسين[2]

[1] قسم الكيمياء الحيوية والأحياء الدقيقة ، كلية الصيدلة ، جامعة البعث ، حمص ، سورية

[2] قسم الكيمياء الحيوية والأحياء الدقيقة ، كلية الصيدلة ، جامعة القلمون ، دير عطية ، سورية

كان الهدف من هذه الدراسة هو تحري بيلة المبيضات عند مرضى الخباثات الدموية، وتحديد العوامل المسببة لها. شملت الدراسة ١٠٠ مريض ممن لديهم أحد الأمراض التالية: الابيضاض النقوي الحاد ((AML، الابيضاض النقوي المزمن ((CML، الابيضاض اللمفاوي الحاد ((ALL، الابيضاض اللمفاوي المزمن ((CLL، الورم النقوي العديد ((MM، لمفوما هودجكن ((HL، ولمفوما لاهودجكن (NHL)الذين تم قبولهم في قسم أمراض الدم في بعض المشافي في مدينة حمص–سورية بين كانون الأول ٢٠٢٠ وأيلول ٢٠٢١. تم تحديد أنواع المبيضات من خلال لون المستعمرة على وسط كروم آغار، اختبار الأنبوب الإنتاشي، والتشكل الدقيق على وسط كورنميال آغار. كان هناك ١٣ (١٣%) من المرضى لديهم بيلة مبيضات. كانت C. albicans السبب الأكثر شيوعاً لبيلة المبيضات (٦١,٥ %)، تلتها C. tropicalis و C. krusei (15.4%)، على التوالي)، ومن ثم C. dubliniensis (7.7%). وفقاً لنتائج التحليل الإحصائي وجد أن بيلة المبيضات ارتبطت ارتباطاً معنوياً مع كل من الجنس الأنثوي، التعرض السابق للقثطرة البولية، الابيضاض النقوي الحاد، وقلة العدلات الشديدة (<٥٠٠ خلية/مم٣).