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Candiduria in hematologic malignancy patients without a urinary catheter: nothing more than a frailty marker?

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Summary

Background—There is scarcity of data regarding significance of candiduria in patients with hematologic malignancies and its association with invasive candidiasis.

Patients and Methods—To that end, we retrospectively evaluated all hospitalized, non-intensive care unit patients with hematologic malignancies and candiduria during a 10-year period (2001-2011). To decrease the possibility of bladder colonization and sample contamination, we excluded all patients with candiduria who had urinary catheters and those with concomitant bacteriuria.

Results—Twenty-four such patients (21 females) were identified, with median age at diagnosis 62 years (range, 20-82 years). Acute leukemia was the most common underlying disease (54%); 62% of these cases were not in remission. Twenty-nine % of the patients had diabetes mellitus and 25% were neutropenic. The most common isolated *Candida* species was *Candida glabrata* (37%), followed by *Candida albicans* (29%). Only 8% of them had urinary tract infection symptoms. However, 88% received systemic antifungals. Candidemia and crude mortality rates at 4 weeks were low (4% and 12%, respectively).

Conclusions—Isolated candiduria in patients with hematologic malignancies has risk factors similar to those in other hospitalized patients, and it does not seem to be a strong predictor of subsequent invasive candidiasis.

Keywords

Candiduria; hematologic; candidiasis; urinary catheter

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Introduction

Candiduria is a commonly encountered finding in hospitalized patients [1]. *Candida* growth in urine may represent contamination, colonization (frequently associated with use of urinary catheters), primary urinary infection, or disseminated mycosis (rarely) [1]. Although the need for treatment of silent, incidental candiduria is controversial, certain conditions require an aggressive approach. These include urologic manipulations, low birth weights, and neutropenia [2]. However, data on the significance of candiduria in patients with hematologic malignancies and its association with invasive candidiasis and survival are scarce.

Patients and Methods

To that end, we retrospectively evaluated all hospitalized, non-intensive care unit (ICU) patients with hematologic malignancies and candiduria who had at least one culture of a clean-voided urine sample that yielded at least 10^3 *Candida* species CFUs [Colony Forming Units]/mL at The University of Texas MD Anderson Cancer Center from January 1st, 2001, to October 1st, 2011. Yeasts were isolated and identified at the genus/species level using standard methods as described previously [3]. To decrease the possibility of bladder colonization and sample contamination, we excluded all patients with candiduria who had urinary catheters and those with concomitant bacteriuria. The patients' electronic records were reviewed for demographic characteristics, underlying hematologic malignancy, laboratory parameters, symptoms, concomitant infections, and prior chemotherapeutic regimens, including corticosteroids in the month prior to candiduria diagnosis. Data regarding concurrent treatment with antibiotics and antifungals administered both at the time of and following candiduria diagnosis were also collected. In addition, development of candidemia and/or renal candidiasis and the mortality rate within 4 weeks after diagnosis were recorded. Neutropenia was defined as a neutrophil count less than $500/mm^3$. Microscopic hematuria and pyuria were defined as more than 10 red blood cells and more than 10 white blood cells per high-power field, respectively, in automated urine microscopy. The study protocol was approved by the MD Anderson Institutional Review Board.

Results

We screened 136 hematological malignancy patients with candiduria and identified 24 (18%) patients who fulfilled the inclusion criteria (Table 1). Of these, only 8 patients (34%) had verification of candiduria in a second urine sample within 3 days after initial diagnosis. The rest of them (66%) were not re-tested. The median age at diagnosis was 62 years (range, 20-82 years), and 21 (88%) of them were female. Seventy-one % were hospitalized more than once during the 6 months prior to candiduria diagnosis (mean total duration of hospitalizations, 12 days [range, 1-55 days]). Acute leukemia was the most common underlying disease (54%); 62% of these cases were not in remission. Twenty-five% of the patients were HSCT (hematopoietic stem cell transplant) recipients, and 29% had diabetes mellitus. Six patients (25%) were neutropenic for an average duration of 28 days prior to candiduria diagnosis (range, 1-120 days), and 50% had recently received chemotherapeutic regimens. Nine patients (38%) had fever, and only 2 patients (8%) reported dysuria, pollakiuria or stranguria.

Twelve patients (50%) were receiving systemic antifungals either at the time of candiduria diagnosis or during the month prior to it (6 patients [25%] for each group were undergoing antifungal prophylaxis and empirical antifungal treatment because of unexplained fever). Moreover, 19 patients (79%) had concomitant infections, most commonly pneumonia, and 83% were receiving antibiotic treatment with 1 or more antimicrobial agents for a mean

duration of 18 days (range, 1-60 days) at the time of candiduria diagnosis. Twenty-five% of the patients had abnormal renal function (glomerular filtration rate <60 ml/min); a small subset of patients reported a previous history of urological abnormalities (2 [8%]) (Table 1) or a history of recent genitourinary surgical procedures (3 [13%]). 17% (4) underwent renal ultrasound after candiduria diagnosis, without finding any abnormalities.

The most common isolated *Candida* species was *Candida glabrata* (9 [37%]) followed by *Candida albicans* (7 [29%]). 88% (21) received antifungal treatment after candiduria diagnosis; of these, 71% (17) received empirical antifungal treatment, whereas the remaining 17% (4) 4 simply continued the antifungal prophylaxis. Of note, 11 patients received empirical antifungal treatment, 7 [64%] with echinocandins. In comparison, 6 patients received antifungals for *Candida* urinary tract infections (UTIs), only 1 of whom [17%] received echinocandins ($P = .13$).

Thirty-three % (8) did not have a follow-up urine culture within 1 month after candiduria diagnosis. Of the remaining 16 patients, 13 (81%) had clearance of candiduria. Only 1 patient (4%) had *C. glabrata* candidemia (25 days after *C. glabrata* funguria diagnosis); this patient was receiving combined caspofungin and voriconazole. Overall, 13% (3) died within 1 month after candiduria diagnosis. Only 1 patient underwent autopsy, which did not reveal invasive candidiasis.

Discussion

Candiduria is rare in healthy individuals [1] and data regarding risk factors for and the natural history of this condition in cancer patients are particularly limited [4]. In the present study, we found that a high rate of our noncatheterized patient population with hematologic malignancies had several known predisposing factors according to what reported in previously published works [1]; the vast majority were elderly female patients with a history of multiple hospitalizations and broad-spectrum antimicrobial agent use. History of diabetes mellitus, renal dysfunction, and recent ICU admission was also common (Table 1). A small subset had additional anatomical risk factors such as urologic abnormalities and prior genitourinary surgical procedures. Nevertheless, urinary catheters seem to remain the most important risk factor for candiduria in hematologic malignancy patients as 75% of the patients had indwelling catheters and were excluded from our study.

Most patients have no symptoms suggestive of UTI, as yeast in the urine frequently indicates merely contamination or colonization. Furthermore, many patients are hospitalized in the ICU, typically with indwelling urinary catheters. Thus, clinical manifestations of candiduria in these patients can hardly be assessed [5]. The presence of pyuria at urinalysis also is not generally considered a useful diagnostic marker of *Candida* UTI, as it may be associated with the presence of a urinary catheter or concomitant bacteriuria [5]. Interestingly, in the present study, only 8% of funguria patients had UTI symptoms, and 38% had fever. In addition, less than 50% of the patients presented with pyuria, which may be attributed to either neutropenia or the mere absence of clinically significant *Candida* UTI. Of note, physicians requested the majority of the urine cultures in our study as part of source-of-fever investigations, even in the absence of urinary complaints, which may explain the higher percentage of undifferentiated fever than that of UTI symptoms. Therefore, in severely ill patients like our patient population, the presence of candiduria often may reflect opportunistic colonization of the urinary tract, not an actual UTI.

The most common *Candida* species in our study was *C. glabrata*, as reported in the published literature [6-8]. Some [9-10] investigators have found prior antifungal use to predict selection of *Candida* spp. Therefore, the high frequency of urinary non-*C. albicans*

spp. in our study mirrors the reported epidemiologic shift in *Candida* fungemias in leukemia units [11-13].

Only 1 patient in our study (4%) developed candidemia, and 4 patients (17%) died within 4 weeks after candiduria diagnosis. In previous studies, investigators also demonstrated low rates of candidemia with high crude mortality rates in patients with candiduria, highlighting that candiduria is not a strong predictor of invasive candidiasis but rather a marker of debilitation and severe underlying disease [6, 14]. The exception is neonates with low birth weights, in whom funguria is known to be synonymous with disseminated candidiasis and warrants systemic antifungal treatment [15].

Our study had several limitations, as we retrospectively collected the data, the cases spanned a decade, the number of patients was small, and we did not use a control group. Of note, the low number of patients with candiduria could also be attributed to the lack of further differentiation of yeasts in the urine samples if this was not asked by the treating clinicians. In addition, the low rate of verification of candiduria (34%) could not preclude that a significant rate of our population had a mere contamination or colonization. Moreover, we assumed that the absence of recorded symptoms meant that these were absent, but it is possible that the health care provider did not record them leading to misclassification bias. The following conclusions may however be made, although future prospective, observational studies are warranted to confirm them:hematologic and non-hematologic hospitalized patients share similar risk factors for isolated candiduria; the latter commonly reflects mere colonization and does not seem to predispose to or predict subsequent invasive candidiasis.

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References

1. Sobel JD, Fisher JF, Kauffman CA, Newman CA. Candida urinary tract infections--epidemiology. Clin Infect Dis. 2011; 52(Suppl 6):S433–6. [PubMed: 21498836]
2. Pappas PG, Kauffman CA, Andes D, et al. Clinical practice guidelines for the management of candidiasis: 2009 update by the Infectious Diseases Society of America. Clin Infect Dis. 2009; 48:503–35. [PubMed: 19191635]
3. Larone, DH. Medically important fungi. 4th ed. ASM Press; Washington, D.C.: 2002.
4. Oravcova E, Lacka J, Drgona L, et al. Funguria in cancer patients: analysis of risk factors, clinical presentation and outcome in 50 patients. Infection. 1996; 24:319–23. [PubMed: 8875285]
5. Kauffman CA, Fisher JF, Sobel JD, Newman CA. Candida urinary tract infections--diagnosis. Clin Infect Dis. 2011; 52(Suppl 6):S452–6. [PubMed: 21498838]
6. Safdar N, Slattery WR, Knasinski V, et al. Predictors and outcomes of candiduria in renal transplant recipients. Clin Infect Dis. 2005; 40:1413–21. [PubMed: 15844063]
7. Paul N, Mathai E, Abraham OC, Michael JS, Mathai D. Factors associated with candiduria and related mortality. J Infect. 2007; 55:450–5. [PubMed: 17706785]
8. Delgado J, Calvo N, Gomis A, et al. Candiduria in renal transplant recipients: incidence, clinical repercussion, and treatment indication. Transplant Proc. 2010; 42:2944–6. [PubMed: 20970578]

9. Harris AD, Castro J, Sheppard DC, Carmeli Y, Samore MH. Risk factors for nosocomial candiduria due to Candida glabrata and Candida albicans. Clin Infect Dis. 1999; 29:926–8. [PubMed: 10589912]

10. Alvarez-Lerma F, Nolla-Salas J, Leon C, et al. Candiduria in critically ill patients admitted to intensive care medical units. Intensive Care Med. 2003; 29:1069–76. [PubMed: 12756441]

11. Horn DL, Neofytos D, Anaissie EJ, et al. Epidemiology and outcomes of candidemia in 2019 patients: data from the prospective antifungal therapy alliance registry. Clin Infect Dis. 2009; 48:1695–703. [PubMed: 19441981]

12. Sipsas NV, Lewis RE, Tarrand J, et al. Candidemia in patients with hematologic malignancies in the era of new antifungal agents (2001-2007): stable incidence but changing epidemiology of a still frequently lethal infection. Cancer. 2009; 115:4745–52. [PubMed: 19634156]

13. Savini VCC, Di Marzio I, et al. Pan-azole-resistant Candida guilliermondii from a leukemia patient's silent funguria. Mycopathologia. 2010; 169:457–9. [PubMed: 20135354]

14. Kauffman CA, Vazquez JA, Sobel JD, et al. Prospective multicenter surveillance study of funguria in hospitalized patients. The National Institute for Allergy and Infectious Diseases (NIAID) Mycoses Study Group. Clin Infect Dis. 2000; 30:14–8. [PubMed: 10619726]

15. Wynn JL, Tan S, Gantz MG, et al. Outcomes following candiduria in extremely low birth weight infants. Clin Infect Dis. 2012; 54:331–9. [PubMed: 22144537]

Table 1

Characteristics of 24 noncatheterized patients with hematologic malignancies and candiduria

Characteristic	*n* (%)
Race	
White	11 (46)
Hispanic	7 (29)
Other[a]	6 (25)
Hematologic malignancy	
AML/MDS	12 (50)
ALL	4 (17)
NHL	2 (8)
CLL	2 (8)
Other[b]	4 (17)
GvHD[c]	2 (8)
Hypoalbuminemia (<3 mg/dl) [c]	8 (33)
Prior immunosuppressive therapy[d,e]	7 (29)
Prior corticosteroid use (>600 mg)[d]	4 (17)
Prior ICU stay[d]	4 (17)
History of urinary tract abnormality[f]	2 (8)
Presence of central venous catheter[c]	15 (63)
Concomitant infection[d,g]	19 (79)
Respiratory tract	12 (50)
Urinary tract[h]	9 (37)
Other[i]	4 (17)
Prior antifungal use[d,j]	12 (50)
Azoles	
Fluconazole	4 (17)
Voriconazole	4 (17)
Posaconazole	1 (4)
Itraconazole	1 (4)
Echinocandins	3 (13)
Caspofungin	2 (8)
Anidulafungin	1 (4)
Urinalysis findings (*n* = 21)	
Proteinuria	16 (76)
Hematuria	3 (14)
Pyuria	9 (43)
Casts	6 (29)
Glycosuria	5 (24)
Nitrites	4 (19)

Characteristic	*n* (%)
Candida species[k]	
C. glabrata	9 (38)
C. albicans	7 (29)
C. tropicalis	6 (25)
C. krusei	1 (4)
C. kefyr	1 (4)
C. parapsilosis	1 (4)

NOTE. AML, acute myeloblastic leukemia; MDS, myelodysplastic syndrome; ALL, acute lymphoblastic leukemia; NHL, non-Hodgkin lymphoma; CLL, chronic lymphocytic leukemia; GvHD, graft-versus-host-disease.

[a] Black (*n* = 5) Asian (*n* = 1).

[b] Multiple myeloma, chronic myelogenous leukemia, aplastic leukemia, and myelofibrosis (one each).

[c] At the time of candiduria diagnosis.

[d] In the month prior to candiduria diagnosis.

[e] Immunosuppressive regimens such as tacrolimus and tumor necrosis factor inhibitor.

[f] The first patient reported a history of ureteric stent placement (4 months before candiduria diagnosis), nephrolithiasis, and recurrent UTIs, and the second underwent ureteric stent placement (5 days before candiduria diagnosis) for ureter obstruction secondary to lymph node enlargement.

[g] Some patients had more than one site of infection.

[h] Coagulase-negative *Staphylococcus* species (*n* = 5), *Enterococcus* species (*n* = 2), *Escherichia coli* (*n* = 1), *Pseudomonas aeruginosa* (*n* = 1), and *Staphylococcus aureus* (*n* = 1) (one patient had 2 different pathogens).

[i] Varicella-zoster virus infection (*n* = 1), acute cholecystitis (*n* = 1), and cellulitis (*n* = 2).

[j] One patient received two different antifungals.

[k] One patient had two different *Candida* spp.