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A case of *Candida glabrata* severe urinary sepsis successfully treated with micafungin

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ABSTRACT

Candida glabrata is frequently resistant to fluconazole, and in advanced renal failure the safe use of this and other recommended drugs is limited. We report a case of a 56 years-old diabetic woman with renal failure and severe urinary sepsis from *C. glabrata* successfully treated with micafungin.

1. Introduction

Symptomatic urinary infections from *Candida species* are frequently encountered in persons with indwelling bladder catheters or in patients immunocompromised for therapy and/or disease. Known additional risk factors for candiduria are female sex and use of antibacterial agents [1].

Candida albicans is the most frequent agent isolated in 50–70% of cases of candiduria, followed by *Candida glabrata* in nearly 20% and *Candida tropicalis* in the remaining [2]. *Candida non-albicans* candiduria, especially *C. glabrata,* is steadily increasing due to widespread use of immunosuppressive agents and azole therapy [3,4].

Treatment of symptomatic candiduria is challenging and selection of antifungal agents is limited. According to guidelines [5,6] established effective treatments of symptomatic candiduria are fluconazole, amphotericin B and flucytosine. However, *C. glabrata* is frequently resistant to fluconazole therapy, and when advanced renal failure is present the safe use of these drugs is of concern and their utility is critically limited. Echinocandins are a class of antifungal agents introduced in the last decade with a broad spectrum of fungicidal activity on *Candida species* [7], however they are rarely considered in urinary tract infections since they do not achieve high urine concentrations [5,7].

We describe a case of severe urinary sepsis from *C. glabrata* successfully treated with micafungin.

2. Case

A 56 years-old woman was admitted to the hospital for high grade fever, dysuria and altered mental status. She was a smoker and had type 2 diabetes mellitus poorly controlled by metformin therapy and inadequate compliance. Her clinical history was irrelevant for other disease and complications of diabetes.

Since 6 days before admission she had had fever and dysuria with opalescent urine. She started treatment with ciprofloxacin 250 mg b.i.d without improvement.

On hospital admission (day 0) she was alert and confabulating, febrile (39.2 °C), tachypnoic, tachycardic (124 bpm) and hypotensive (90/56 mmhg in both arms) with signs of dehydration. Central venous pressure was 5 cmH2O, after fluid replacement with crystalloids arterial blood pressure rose to 123/75 mmhg. After bladder catheterization pyuria was evident. Blood and urine cultures were collected. Laboratory exams were relevant for the presence of leukocytosis, renal failure, severe hyperglycemia (Table 1) with glycosuria (150 mg/dL) and leukocyturia (5609/μL). A complete abdomen ultrasound study and chest X-ray were normal. Large amount fluid replacement was continued, while wide spectrum antibiotic therapy with meropenem (3 g/daily), levofloxacin (500 mg/daily) and insulin treatment was started. After transfer to the Medical High Dependency Unit of the same hospital she continued treatment achieving a good hemodynamic response over the following hours. She had improvement in clinical conditions and the glycemic profile normalized during the following days. Renal function ameliorated even if it remained abnormal (creatinine clearance 48 mL/min). Despite this, she continued to have fever and pyuria. On day +4 blood and urine cultures (> 10^7 CFU/mL) turned positive for *C. glabrata* infection

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Table 1
Relevant serum biochemical parameters on admission and during in-hospital stay.

	On admission	7 Days	14 Days	25 Days	Reference values
WBC ($\times 10^9$/L)	15.80	12.00	12.40	7.51	4.0–10.0
PCT (ng/mL)	8.47	3.87	0.58	0.09	< 0.5
Creatinine (mg/dL)	6.41	3.51	1.58	1.37	0.44–0.90
Azotemia (g/L)	4.40	3.11	0.89	0.55	0.1–0.5
Albumin (g/L)	25.6	–	37.5	–	35–52
Glycemia (g/L)	6.79	1.70	1.84	1.33	0.65–1.10
Sodium (mEq/L)	118	139	135	139	135–146
Potassium (mEq/L)	8.6	5.0	3.5	4.1	3.5–5.3
ALT (UI/L)	8	12	12	9	5–40
AST (UI/L)	7	15	20	12	5–40
GGT (UI/L)	23	18	83	61	10–40
ALP (UI/L)	158	116	–	97	55–130
Bilirubin (mg/dL)	0.15	0.16	–	0.31	0.3–1.0

WBC: white blood cells; PCT: procalcitonin; ALT: alanine transaminase; AST: aspartate transaminase; GGT: gamma-glutamyltransferase; ALP: alkaline phosphatase.

resistant to fluconazole (MIC 256 μg/mL). There were no signs of ocular candidiasis on ophthalmic examination. Antibacterial treatment was stopped and micafungin at the dose of 200 mg daily was added. On day +6 fever disappeared, while candiduria and candidemia cleared after 12 days of micafungin treatment (day +15). Micafungin was continued for a total of 25 days, and stopped on day +29. During that time antifungal treatment was well tolerated and repeated blood exams did not show alterations of liver enzymes. During the hospital stay dysfunction of the bladder due to diabetic dysautonomia was suspected in view of clinical history and repeated unsuccessful attempts to remove urinary catheter.

The patient was discharged home (day +29) on insulin treatment and with indication to intermittent bladder catheter voiding. At 4 months follow-up the patient was in good clinical condition, glycometabolic control improved (HbA1c 82 vs 120.0 mmol/mol) as well as urinary incontinence with no recurrence of candiduria.

3. Discussion

Established effective treatment of symptomatic Candiduria are amphotericin B, fluconazole and flucytosine [5,6]. However, in the presence of renal failure these agents are contraindicated or at risk of significant toxicity and their utility are substantially limited. Moreover, fluconazole is extensively excreted by kidneys reaching high urinary concentrations but, as well known, *C. non-albicans species* and notably *C. glabrata* are nowadays frequently resistant to fluconazole therapy.

Echinocandins are potent antifungal agents that exert their activity by inhibiting beta-(1,3)-D-glucan synthase, an enzyme that is necessary for the synthesis of glucan, a major component of the fungal cell wall [7,8]. Micafungin, like the entire class of echinocandin drugs, has a broad spectrum of activity on *Candida species* and it is now considered a first-line therapy in candidiasis. In general micafungin is well tolerated, has a low potential of drug interactions, its clearance is independent from glomerular filtration and there are no contraindications or needing for dose adjustment even in severe renal failure. All echinocandins are highly protein bound (99%) and share the major pharmacokinetic disadvantage of poor glomerular filtration and tubular secretion resulting in very low urinary concentrations [7,8]. For that reason, even if they have a very favorable profile in terms of efficacy and safety, their use seems precluded in fungal urinary tract infections. However, despite micafungin is minimally excreted in urine, it has been shown in animal models a wide distribution in many organs and tissues, including kidneys. Experimental models on tissue distribution of micafungin in rabbits and rats showed that after intravenous administration of single or multiple doses of the drug, concentration in kidney tissue was similar to those of plasma, liver and spleen [9,10]. The observed tissue concentrations were several-fold in excess of the MIC against clinical isolates of *Candida spp.* and *Aspergillus spp.*

There are few reports in the literature, a total of 9 cases, on the safe and effective use of echinocandins (i.e. caspofungin and micafungin) in candiduria [11,12] due to *C. glabrata*, *C. tropicalis* and *azole-resistant C. albicans*. Of these, six were cases of candiduria successfully treated with caspofungin. They were collected by Merck Research Laboratories retrospectively from a phase II–III clinical study and three of these, were cases of candiduria secondary to renal candidiasis complicating candidemia in severely ill patients. To our knowledge, only three cases of candiduria treated with micafungin are reported in literature. All patients were immunosuppressed for several reasons and had isolated candiduria without systemic infection, differently from the case herein presented, and responded favorably to micafungin treatment at doses of 50–100 mg/day.

There are some features of this case that should be pointed out. Firstly the patient was treated with a dose of 200 mg daily of micafungin, a dose higher than the standard recommended dose, without adverse effects. The choice of using a dosage greater than usual was empirical, and was motivated by the possibility of achieving higher renal tissue concentration with such dosage. Furthermore, 200 mg is the higher daily dose indicated by micafungin summary of product characteristics in invasive candidiasis not responding to standard dosage. Nextly, in this case significant hypoalbuminemia on hospital admission was present and we could speculate that micafungin unbound to serum albumin was higher than usual, thus achieving greater renal filtration and urinary secretion. Unfortunately in our hospital we were not able to dose urinary concentration of micafungin to support this hypothesis. Nevertheless these two elements could explain a higher than usual urinary concentrations of the drug, and thus its clinical efficacy in eradication of *C. glabrata* infection.

In conclusion the present case shows that micafungin can achieve clinically relevant fungal sterilization even in urine and there is room to consider micafungin in the armamentarium against *C. glabrata* urinary infections, notably in the context of renal failure where other antifungal effective drugs are unsafe or contraindicated.

Conflict of interest

None of the authors declare conflict of interest pertaining to this case report. Astellas Pharma (Assago, Milan, Italy) supported this publication with an unconditional support. Astellas had no role in managing the case, collecting and interpreting data, conceiving and writing the manuscript.

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