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CASE REPORT/CAS CLINIQUE

Caspofungin irrigation through percutaneous calicostomy catheter combined with oral flucytosine to treat fluconazole-resistant symptomatic candiduria

Traitement d'une candidurie symptomatique résistante au fluconazole par irrigation de caspofungine via une pyélostomie et flucytosine per-os

H. Garcia [a], J. Guitard [b], J. Peltier [a], M. Tligui [c], S. Benbouzid [c], S. Ait Elhaj [a], E. Rondeau [a], C. Hennequin [b,*]

[a] *Service de néphrologie et transplantation rénale, hôpitaux universitaires de l'Est-Parisien, hôpital St-Antoine, 184, rue du Faubourg St-Antoine, 75012 Paris, France*
[b] *Service de parasitologie-mycologie, hôpitaux universitaires de l'Est-Parisien, hôpital St-Antoine, 184, rue du Faubourg St-Antoine, 75012 Paris, France*
[c] *Service d'urologie, hôpitaux universitaires de l'Est-Parisien, hôpital St-Antoine, 184, rue du Faubourg St-Antoine, 75012 Paris, France*

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Summary Candiduria may be a marker of serious fungal infections such as pyelonephritis. With the exception of fluconazole and flucytosine, antifungals drugs are not excreted into the urine as active drugs, making the management of infection due to fluconazole-resistant *Candida* difficult. We report a case of recurrent *Candida parapsilosis* candiduria in a kidney transplant recipient suffering from chronic ureteral obstruction requiring permanent ureteral catheterization (double-J stent). Attempts to remove the stent led to pyelonephritis episodes during which only *Candida* was isolated from the urine. Following several courses of azole-based therapy, the causative agent became resistant to fluconazole. Clinical and mycological cure were obtained combining irrigations of caspofungin through a percutaneous calicostomy catheter and oral

* Corresponding author. Service de parasitologie-mycologie, hôpitaux universitaires de l'Est-Parisien, hôpital St-Antoine, 184, rue du Faubourg St-Antoine, 75012 Paris, France.
E-mail address: christophe.hennequin@upmc.fr (C. Hennequin).

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flucytosine. This strategy may represent an interesting therapeutic alternative in case of fluconazole-resistant symptomatic candiduria.

MOTS CLÉS
Candida ;
Candidurie ;
Resistance aux azolés ;
Caspofungine ;
Irrigation locale

Résumé Bien que souvent asymptomatique, la candidurie peut témoigner d'infections sévères comme les pyélonéprites candidosiques. Hormis le fluconazole et la flucytosine, les antifongiques systémiques ne sont pas éliminés sous forme active dans les urines. En cas d'infection à germe fluconazole-résistant, le traitement de ces infections devient alors difficile. Nous rapportons le cas d'une candidurie récurrente à *Candida parapsilosis* chez un patient transplanté rénal présentant une obstruction urétérale nécessitant un cathétérisme permanent des voies urinaires par sonde double-J. L'ablation répétée du matériel étranger conduisait à des épisodes de pyélonéphrite pour lesquels, seule la levure était isolée des urines. Après plusieurs cures de traitement par dérivés azolés, la souche devenait résistante à ces molécules mais restait sensible aux échinocandines. Un traitement combinant irrigation de caspofungine à travers une pyélostomie et flucytosine per-os permettait une guérison clinique et une éradication mycologique de la levure malgré le maintien de la sonde double-J. Cette stratégie représente une alternative thérapeutique intéressante en cas de candidurie par une souche résistante au fluconazole.

Introduction

Candiduria is one of the most common nosocomial infections [13]. Patients with foreign material in urinary tract, notably kidney transplant recipients, are at a particularly high risk [12]. Although most of these infections are asymptomatic, some patients will develop typical clinical features of cystitis. More rarely, candiduria may result in obstruction that may possibly be complicated by urinary sepsis with a possible renal parenchymal involvement and even candidemia [8,5]. In these cases, therapeutic approach, apart from external material withdrawal, is challenging because only fluconazole and flucytosine have activity in the urine [9]. Thus, this condition may represent almost a therapeutic impasse when the causative agent is or becomes resistant to these drugs. We report on the use of local-irrigation of caspofungin in the case of a double-J stent-associated candiduria due to a fluconazole-resistant *Candida parapsilosis* strain.

A 39-year-old male presented in January 2013 to our institution with a 2-day history of dysuria and oliguria. In 2006, he underwent a renal transplantation that further complicated with chronic distal ureter stenosis leading to recurrent obstructive acute kidney injuries or urosepsis requiring multiple double-J catheterizations. A first episode of candiduria due to *C. parapsilosis* was observed in May 2011 (Table 1). During the following months, he relapsed several times, and following several courses of fluconazole and voriconazole, the strain became resistant to azole derivatives. On admission, his temperature was 36.8 °C, his blood pressure was at 125/80 mmHg. Physical examination only revealed graft tenderness in the right iliac fossa. Laboratory evaluation showed elevated creatinine serum level at 4.54 mg/dL. There was also a mild neutrophilia (8.2×10^9/L), and an elevated C-reactive protein plasma concentration at 208 mg/L (reference < 4.0 mg/L). Ultrasonography demonstrated hydronephrosis of the kidney graft (renal pelvis 24 mm and ureter 12 mm) despite the correct *in situ* position of a double-J stent.

The patient was treated empirically with piperacillin/tazobactam, vancomycin and oral fluconazole at 200 mg per day. *C. parapsilosis* grew in pure culture from a sample of the renal calix urine. Blood cultures remained negative. Antibiotics were withheld, and fluconazole was changed on day 3 to intravenous caspofungin (70-mg loading dose followed by 50 mg daily). However, urine culture remained positive. Since ultrasonography still showed signs of obstruction, a percutaneous calicostomy was performed on day 12. Double-J stent was changed again on day 17. Because candiduria persisted, an antifungal combination therapy with oral 5-flucytosine (500 mg bid) and continuous irrigation of caspofungin through percutaneous calicostomy catheter (50 mg in 100 mL 0.9% sodium chloride infused during 24 hours) was begun on day 20. Because an ureteroplasty was planned in order to permanently remove any foreign material in the urinary tract and prevent any recurrence of candiduria or urosepsis, the therapy was continued until day 67 when the patient was discharged. On day 23, urine culture turned negative and remained negative. On day 46, an intravenous pyelogram confirmed the persistence of the stenosis of distal ureter. Weekly blood cell count surveillance did not show any sign of toxicity of 5-flucytosine. Creatinine at discharge was stable at 2.2 mg/dL. Ureteroplasty was performed 2 months later. During a 2-year follow-up, all urine cultures performed routinely remained negative for *Candida*.

Therapeutic management for candiduria depends on the occurrence of clinical manifestations and the presence of underlying predisposing factors for bloodstream dissemination [1]. Immunosuppression, indwelling catheters and ureteral stenosis classified our patient at high risk of dissemination [10]. When antifungal therapy is mandatory, therapeutic options are limited because of the poor urinary diffusion of the active form of most of the antifungal drugs, including the new triazole derivatives and the echinocandins [9,1]. About 20% of amphotericin B administered intravenously is excreted in the urine [4], but renal toxicity limits the use of this drug, particularly in patients with underlying