Case Report

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Persistent *Candida parapsilosis* funguria associated with an indwelling urinary tract stent for more than 7 years

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Candiduria is an increasingly common condition, and the lack of effective antifungal treatment in many cases has raised great concern. We report a case of persistent *Candida parapsilosis* funguria associated with urinary tract instrumentation. Molecular typing suggested that during a 7 year period the *C. parapsilosis* isolates were all the same strain. Prolonged antifungal therapy and regular catheter replacement failed to eradicate the funguria, but improved urinary symptoms and pyuria. The antifungal susceptibility pattern did not significantly change during the clinical course despite repeated exposure to fluconazole.

Introduction

Candiduria is an increasingly common condition, especially in hospitalized patients (Lundstrom & Sobel, 2001; Shay & Miller, 2004; Toya *et al.*, 2007). It is often difficult for clinicians to distinguish between colonization and infection in these patients (Lundstrom & Sobel, 2001). The lack of effective antifungal treatment in many cases has also raised great concern (Sobel *et al.*, 2000).

Case report

A 51-year-old man developed stricture of the bilateral ureteral valve due to urinary tuberculosis in December 2000. He received anti-tuberculosis therapy for 1 year after diagnosis. However, tuberculosis-related obstructive uropathy with hydronephrosis and hydroureter were noted. In January 2001, bilateral double-J stents were inserted for the treatment of the ureteral stricture and were replaced regularly every 3 months. Routine replacement of double-J stents every 3 months is a standard procedure at the National Taiwan University Hospital. The result of baseline urinalysis performed after insertion of the double-J stents revealed mild pyuria, and a serum creatinine level of approximately 2 mg dl⁻¹. In February 2001, *Candida parapsilosis* funguria was detected for the first time. However, the patient did not receive antifungal therapy until November 2001 due to progressive dysuria and pyuria. The pyuria improved with the administration of daily oral fluconazole (200 mg), but funguria with high colony counts (>10 000 c.f.u. ml⁻¹) persisted despite

fluconazole treatment and concurrent replacement of catheters. An increase in the fluconazole dose to 300 mg per day did not eradicate the funguria. Fluconazole was discontinued several months later, and the *C. parapsilosis* funguria persisted. Renal sonography showed mild bilateral hydronephrosis but no fungal ball or other marked abnormalities. Subsequently, the patient received several courses of fluconazole treatment due to the presence of symptomatic *C. parapsilosis* funguria. In 2006, the patient was treated with caspofungin for 14 days and oral voriconazole for 7 days for the eradication of the *C. parapsilosis* funguria; however, this treatment strategy also failed. Thereafter, the patient received further courses of oral fluconazole treatment several times as the urinary symptoms and pyuria progressed. For 7 years, i.e. until November 2007, this patient underwent double-J stent replacement 24 times and experienced more than 10 episodes of *C. parapsilosis* funguria with high colony counts (>10 000 c.f.u. ml⁻¹). Culture of the removed double-J stents was found to be positive for *C. parapsilosis* on several occasions. In November 2007, the urine culture still yielded *C. parapsilosis* with colony counts >10 000 c.f.u. ml⁻¹. However, despite the persistent *C. parapsilosis* funguria, the patient did not acquire ascending infection or disseminated disease during this period. The patient was followed-up regularly at our outpatient clinic and had few urinary tract symptoms. At the time of this study, the patient continued to undergo double-J stent replacement every 3 months.

The four isolates of *C. parapsilosis* that were recovered from the urine specimens of this patient in 2001 and 2007 were preserved in the microbiology laboratory of the National Taiwan University Hospital. Antifungal susceptibility testing

Abbreviation: RAPD, random amplified polymorphic DNA.

was performed using the reference broth microdilution method according to the guidelines of Clinical and Laboratory Standards Institute (CLSI, 2002). Two reference strains, *C. parapsilosis* ATCC 22019 and *Candida krusei* ATCC 6258, were used as quality control strains. MICs were determined after incubation for 48 h. The susceptibility testing results of the four *C. parapsilosis* isolates are shown in Table 1. All the isolates were susceptible to fluconazole (MICs 1–4 $\mu\text{g ml}^{-1}$) and amphotericin B (MICs 1 $\mu\text{g ml}^{-1}$). MICs of the four isolates were within twofold dilution variation for other agents tested. Random amplified polymorphic DNA (RAPD) patterns of the isolates were determined by arbitrarily primed PCR. The four oligonucleotide primers used, 3 (5'AGTCAGCCAC 3'), H12 (5'ACGCGCATGT 3'), H15 (5'AATGGCGCAG 3') and M13 (5'GAGGGTGGCGGTTCT 3'), were purchased from Operon Technologies. Identical RAPD patterns indicated that all the isolates belonged to the same strain (Fig. 1).

Discussion

Candiduria has become an increasingly common problem in hospitalized patients (Lundstrom & Sobel, 2001; Shay & Miller, 2004; Toya *et al.*, 2007). The risk factors for candiduria include urinary tract instrumentation, diabetes mellitus, malignancy, recent antibiotic therapy and old age (Hamory & Wenzel, 1978; Kauffman *et al.*, 2000). Differentiating between *Candida* infection and colonization is difficult in cases where candiduria alone is detected (Lundstrom & Sobel, 2001). In most patients, the isolation of *Candida* species from urine samples is indicative of benign colonization. The principles regarding when to treat, whom to treat and how long to treat are still controversial (Lundstrom & Sobel, 2001). In the present case, mild pyuria was noted upon baseline urinalysis, which was considered to be related to the placement of double-J catheters. Both the severity of pyuria and the colony count of *Candida* in urine were used to guide treatment. However, candiduria could not be resolved successfully despite a prolonged course of fluconazole and the regular replacement of indwelling catheters. Molecular

Table 1. MICs of four *C. parapsilosis* isolates to seven antifungal agents

Antifungal agent	MIC ($\mu\text{g ml}^{-1}$)			
	Date isolate obtained (month/year):			
	2/2001	6/2007	7/2007	11/2007
Fluconazole	1	4	2	4
Itraconazole	0.25	0.12	0.12	0.25
Voriconazole	0.03	0.12	0.06	0.06
Amphotericin B	1	1	1	1
Caspofungin	1	1	1	1
Micafungin	1	1	1	0.5
Anidulafungin	0.5	1	0.5	0.5

Fig. 1. RAPD patterns of four *C. parapsilosis* isolates from our patient (lanes 1–4) and two *C. parapsilosis* isolates from different patients (lanes 5–6) used as controls. Identical RAPD patterns in lanes 1–4 indicated these isolates belonged to the same strain.

typing suggested that the same strain of *C. parapsilosis* was isolated from the urine of the patient before and after the administration of antifungal treatment and throughout the 7 year clinical course. Voriconazole and caspofungin administration also failed to eradicate candiduria despite the high *in vitro* potency of these antifungal drugs.

Although not proved by microscopic methods, the formation of a biofilm was considered as the cause of the persistent candiduria in this patient. It is well known that indwelling medical devices can support *Candida* colonization and biofilm formation, and that the biofilm cells are relatively resistant to antifungal treatment (Kojic & Darouiche, 2004). The process of fungal biofilm development, which involves adherence to device surfaces, morphogenic conversions, extracellular matrix production and induction of drug-resistance, has been described in detail (Blankenship & Mitchell, 2006; Ramage *et al.*, 2005). Due to the unique characteristics of the *Candida* biofilm, *in vitro* susceptibility to antifungal agents cannot guarantee efficacy of the use of these agents in the clinical treatment of candiduria, as illustrated in the present case.

Other studies have also demonstrated the minimal benefits of antifungal therapy for eradicating *Candida* funguria

(Kauffman *et al.*, 2000; Sobel *et al.*, 2000). These findings do not mean that antifungal therapy is unnecessary for patients with candiduria; however, the treatment should not be expected to eradicate the organism. The Infectious Diseases Society of America has suggested that the treatment goal should be to eliminate the associated signs and symptoms, and reduce the risk of ascending or disseminated infection (Pappas *et al.*, 2004). Furthermore, catheter change alone rarely results in the clearance of candiduria, but the discontinuation of catheter use may help eradicate this infection (Kauffman *et al.*, 2000).

Despite repeated exposure to fluconazole, the *C. parapsilosis* isolates in the present study remained susceptible to fluconazole (Table 1). The antifungal susceptibility pattern of each isolate was unremarkable except for a mild increase in the MIC of fluconazole after treatment. Similar observations have been reported in a another study (Clancy *et al.*, 2000).

In conclusion, we report a case of persistent and difficult-to-treat *C. parapsilosis* funguria associated with urinary tract instrumentation. During a 7 year period, the patient had 10 episodes of funguria caused by the same strain of *C. parapsilosis*. Prolonged antifungal therapy and regular catheter replacement failed to eradicate the funguria but improved urinary symptoms and pyuria. The antifungal susceptibility pattern did not significantly change during the clinical course despite repeated exposure to fluconazole.

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