Treatment of candiduria with micafungin: A case series

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There has been a gradual increase in the incidence of non-*Candida albicans*-related nosocomial infections. *Candida glabrata* urinary tract infections have increased in frequency, and treating these infections can be difficult because the organism may be resistant to fluconazole. A newer antifungal agent, micafungin, which belongs in the class of echinocandins, provides an alternative and effective therapy against *C glabrata*. The present report describes three cases of *C glabrata*-associated urinary tract infections successfully treated with micafungin. To the authors' knowledge, this is the first report of successful treatment of *C glabrata* and azole-resistant *C albicans*-associated urinary tract infection with an echinocandin.

Key Words: *Candiduria*; *Echinocandins*

The causative species producing candiduria in adults are similar in most studies. *Candida albicans* accounts for 50% to 70% of all *Candida*-related urinary isolates, followed by *Candida glabrata*, which comprises 20% of isolates, and *Candida tropicalis*, which is the third most common species (1). There has been a steady increase in the incidence of non-*albicans* strains producing nosocomial infections (2-4). Notably, *C glabrata* candiduria has increased in frequency following the widespread and increased use of immunosuppressive agents and broad-spectrum antifungal agents (5). *C glabrata* in the urine is of special importance due to its increased resistance to fluconazole (6,7). Furthermore, fluconazole use has been associated with *C glabrata* candiduria but not with *C albicans* candiduria. No other specific epidemiological risk factors for *C glabrata* urinary tract infection have been reported. Diabetes mellitus, indwelling bladder catheter, female sex and the use of antibacterial agents have been risk factors identified for both *C glabrata* and *C albicans* candiduria (8).

The echinocandins are a class of antifungal agents that provide an alternative and effective therapy against *C glabrata*. Like other echinocandins, micafungin (Mycamine, Astellas Pharma, Inc, USA) inhibits glucan synthesis, an enzyme required for the synthesis of a major fungal cell wall component, 1-3-beta D-glucan, and interferes with fungal cell wall

Traitement de la candidurie à la micafungine : série de cas

Il y a eu une augmentation graduelle des infections nosocomiales à d'autres germes que *Candida albicans* au fil du temps. La fréquence des infections urinaires à *Candida glabrata* est plus élevée qu'avant et il peut être difficile de traiter ces infections parce que le micro-organisme en cause peut se montrer résistant au fluconazole. Un nouveau médicament antifongique, la micafungine, qui appartient à la classe des échinocandines, offre un traitement de rechange efficace contre *C glabrata*. Le présent rapport fait état de trois cas d'infection urinaire à *C glabrata*, traités avec succès à la micafungine. D'après les auteurs, il s'agirait là du premier rapport de traitement réussi d'infections urinaires à *C glabrata* et à *C albicans* résistant aux azoles, à l'aide d'une échinocandine.

synthesis (9). Although metabolized in the liver, micafungin may be useful in the treatment of candiduria. The present report describes our experience with micafungin in the treatment of persistent urinary tract infections associated with *C glabrata* and fluconazole-resistant *C albicans*.

CASE PRESENTATIONS

Case 1

A 39-year-old woman with type 1 diabetes mellitus developed urinary dysuria, frequency, urgency and pelvic discomfort shortly after renal transplantation. Her immunosuppressive therapy included mycophenolate mofetil, tacrolimus and prednisone. Although kidney and bladder ultrasound did not show evidence of obstruction or fungal ball, a urine culture produced more than 100×10^6 colony-forming units (CFU)/L of *C glabrata*, for which she received a six-week course of fluconazole 200 mg daily (orally).

Three months after transplantation, the symptoms of cystitis recurred, without systemic features. *Klebsiella pneumoniae* and *C glabrata* were cultured in urine. Despite treatment with oral ciprofloxacin 250 mg twice daily for 14 days, the patient remained symptomatic. She then received a 10-day course of intravenous ceftriaxone 1 g daily, followed by 14 days of oral cefixime 400 mg once daily. Following this treatment, there was still no resolution in her symptoms.

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Urine cultures were repeated and *C glabrata* was resistant to fluconazole (minimal inhibitory concentration [MIC] 256 µg/mL) and itraconazole (MIC greater than 16 µg/mL), but sensitive to 5-flucytosine (MIC less than 0.03 µg/mL) and amphotericin B (MIC 0.25 µg/mL). At this time, a bladder ultrasound demonstrated a fungal ball, which was removed by cystoscopy.

Due to residual symptoms of cystitis, a urine culture was sent seven days following the procedure. It demonstrated more than 100×10^6 CFU/L of *C glabrata*. The patient received a 14-day course of intravenous micafungin 50 mg daily. A complete resolution in her symptoms ensued, and her energy level and appetite returned to baseline. A urine culture performed seven and 90 days after the last micafungin dose revealed no significant growth. Her tacrolimus level remained within the therapeutic range at 6.1 ng/mL to 10.1 ng/mL (reference trough therapeutic range 5 ng/mL to 15 ng/mL).

Case 2

A 75-year-old woman who had a longstanding history of primary Sjögren's syndrome with associated cutaneous vasculitis, renal insufficiency and pulmonary hypertension presented with a two-month history of malodorous and cloudy urine. She was otherwise asymptomatic. She recently had received a seven-day course of cloxacillin for recurrent pyoderma gangrenosum and associated cellulitis. Her medications included azathioprine and prednisone. No physical findings were evident. More than 100×10^6 CFU/L of *C glabrata* were identified in two urine cultures. The patient was treated with a 14-day course of intravenous micafungin 50 mg daily, after which her symptoms resolved. Repeat urine cultures at one and 24 months after completion of micafungin therapy revealed no significant growth.

Case 3

A 43-year-old man with a history of glomerulonephritis, aortic valve replacement and three renal transplants was seen for the management of persistent candiduria. Following his third transplant in 1998, he had taken ciprofloxacin 500 mg once daily for recurrent bacteriuria and multiple courses of oral fluconazole for persistent candiduria. He was otherwise asymptomatic. There were no fevers, chills or night sweats. His other medications included prednisone 10 mg once daily, mycophenolate mofetil 750 mg twice daily, tacrolimus 1 mg twice daily, amlodipine 10 mg once daily, ramipril 1.25 mg once daily and coumadin 2 mg once daily, as well as an albuterol inhaler and acetaminophen or oxycodone as needed.

Urine cultures persistently revealed more than 100×10^6 CFU/L of *C albicans* resistant to fluconazole (MIC 256 µg/mL). Following a three-week treatment course with intravenous micafungin, the results of the laboratory investigations were all within normal range. His tacrolimus level remained within the therapeutic range at 7.1 ng/mL to 12.1 ng/mL. At one and three months following the treatment, urine cultures showed no growth.

DISCUSSION

Candiduria can be treated with amphotericin B bladder irrigation, provided there is no upper tract infection; it may also be

effectively treated with systemic amphotericin B or fluconazole (10). However, given the adverse effects of amphotericin B and reduced susceptibility to fluconazole, an alternative to these agents is a valuable addition to existing treatment options.

Micafungin has a broad spectrum of activity against *Candida* species, including azole-resistant *C albicans* (11). However, like other echinocandins, it is less active against *Candida parapsilosis* (12).

Micafungin possesses a minimal side effect profile and low potential for drug interactions. Moreover, clearance of micafungin is not renal dependent, and the dosage does not have to be adjusted in patients with renal impairment.

CONCLUSION

The present case reports provide new data on the use of echinocandins such as micafungin for the treatment of fungal urinary tract infections. Thus, echinocandins such as micafungin may prove to be effective and safe alternatives for the treatment of *C glabrata* and other less susceptible strains that produce candiduria (10).

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