CASE REPORT

Treatment of candiduria with micafungin: A case series

Danny Lagrotteria MD FRCPC1, Coleman Rotstein MD FRCPC1, Christine H Lee MD FRCPC1,2,3


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: Candida; 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 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.

1Department of Medicine, McMaster University; 2Hamilton Regional Laboratory Medicine Program; 3Department of Pathology and Molecular Medicine, McMaster University, Hamilton, Ontario
Correspondence: Dr Christine H Lee, Department of Pathology and Molecular Medicine, McMaster University, St Joseph's Healthcare, 50 Charlton Avenue East, Hamilton, Ontario L8N 4A6. Telephone 905-521-6021, fax 905-521-6083, e-mail clee@mcmaster.ca
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Urinary 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 $10^6$ 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 7.1 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 and associated cellulitis. Her medications included asazithoprine and prednisone. No physical findings were evident. More than $10^6$ 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, amiodipine 10 mg once daily, raminipril 1.25 mg once daily and coumadin 2 mg once daily, as well as an alburterol inhaler and acetaminophen or oxycodone as needed.

Urinary cultures persistently revealed more than $10^6$ 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.

**REFERENCES**