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CASE REPORT

Breakthrough disseminated cryptococcosis during micafungin therapy

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Echinocandins are not active against basidiomycetous yeasts, such as *Cryptococcus neoformans*, *Trichosporon*, and *Rhodotorula* species, and zygomycosis. We present a patient with renal failure and candidemia, who developed a breakthrough fungal infection with cryptococcemia and cryptococcuria while receiving micafungin therapy.

Introduction

Cryptococcus neoformans is one of the most common opportunistic infections in AIDS patients.[1] Concurrent infections of cryptococcemia and cryptococcuria (disseminated cryptococcosis) can occur in other non-AIDS immunocompromised patients, such as those with transplant-related immunosuppression, corticosteroid, cancer chemotherapy, systemic lupus erythematosus (SLE), or chronic renal failure.[1—4] The lungs and the central nervous system are the most common sites of cryptococcal infection. Amphotericin B and fluconazole have been the antifungal agents extensively used for yeast infections. The availability of echinocandin may provide an effective treatment with less toxic effects. However, echinocandin is not effective against basidiomycetous yeasts, such as *C. neoformans*, *Trichosporon*, and *Rhodotorula* species.[1,5] We report a patient with chronic renal failure and candidemia who developed cryptococcemia and cryptococcuria (disseminated cryptococcosis) while receiving micafungin therapy.

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Case report

A 77-year-old male patient suffered from fever and disturbed consciousness for 1 day. The patient had been diagnosed with chronic obstructive pulmonary disease and diabetic nephropathy with chronic kidney disease. On admission, the following were noted: body temperature, 39°C; white blood cell count, 30,450 cells/μL; neutrophil, 90%; platelet count, 189,000/μL; and hemoglobin, 8.9 g/dL. Serum biochemical panel revealed blood urea nitrogen 58 mg/dL, creatinine 3.6 mg/dL, total bilirubin 1.8 mg/dL, alanine aminotransferase 56 U/L, and aspartate aminotransferase 80 U/L. Chest roentgenogram showed emphysematous change and minimal bibasilar interstitial infiltration without active lung lesion. He received lumbar puncture examination to rule out meningitis. Cerebral spinal fluid (CSF) studies revealed the following results: glucose, 98 mg/dL (blood glucose, 102 mg/dL); protein, 16 mg/dL; white blood cell count, 1/μL; negative finding by India ink stain. Cryptococcal antigen was negative in blood and CSF. Serum anti-human immunodeficiency virus (HIV) test was negative.

The patient started to receive intravenous teicoplanin, at 600 mg and then 400 mg once daily, and intravenous ceftriaxone (2 g, once daily empirically). He received total parenteral nutrition through central venous catheter (CVC) for septic condition and abdominal ileus. Abdominal computed tomography scan revealed a stone at the left lower third ureter with obstructive uropathy. Urinary analysis revealed pyuria and ceftriaxone was shifted to levofloxacin 750 mg intravenously every other day for suspected complicated urinary tract infection. Hemodialysis was performed through a double lumen for acute renal failure with oliguria. On the 14th hospital day, blood and CVC tip cultures showed the presence of *Candida albicans*. Cardiac echogram found no valvular vegetation. He started to receive intravenous micafungin 200 mg and then 100 mg once daily and became afebrile 2 days later. Repeated blood cultures showed no growth 7 days later.

After 12 days of micafungin therapy, he had dyspnea and fever again. Urinary analysis found pyuria and some budding yeastlike microorganisms. Concurrent blood and urine cultures revealed *C. neoformans*, and serum cryptococcal antigen became positive at a titer of 1:64. A second lumbar puncture was performed, but CSF cryptococcal antigen and fungal culture yielded negative results. API 20C (identification kit of candida species) (bioMe'rieux, Marcy l'Etoile, France) was used for the species differentiation of the isolated yeast.[6] He received intravenous fluconazole therapy (400 mg, once daily) immediately when fungemia was noted. Repeated blood and urine fungal cultures were sterile 7 days later. However, 2 weeks later he died of septic shock with *Acinetobacter baumannii* bacteremia and pneumonia in spite of intravenous fluconazole and cefoperazone/sulbactam (2 g/1 g every 12 hours) treatment.

Discussion

Fungal infection is an important cause of morbidity and mortality in critically ill patients. Cryptococcal disease is a fungal infection that mainly affects immunocompromised hosts. The lungs and the central nervous system are the common sites of cryptococcal infections.[2] According to the study of Lin et al, [7] patients without HIV infection were more likely to have pulmonary involvement and no underlying disease at diagnosis.

Our patient had renal failure and a femoral CVC in place. He suffered from catheter-related candidemia with micafungin therapy first and then disseminated cryptococcosis. In this patient, there were two possible causes for healthcare-associated cryptococcosis. One is the contamination or colonization of the CVC.[2] For example, *Cryptococcus parapsilosis* fungemia had been well documented to be related to CVCs. *C. neoformans* is an environmental yeast, and contamination or colonization of the CVC and subsequent cryptococcemia may be a reasonable cause. Martinez et al[8] demonstrated that fungal biofilm can form on polystyrene plates and medical devices. Another source is the reactivation of occult pulmonary lesions due to immunosuppression contributed by renal failure, steroid therapy, and old age. There has been a report of a patient receiving antitumor necrosis factor-alpha therapy whose condition was complicated with pulmonary cryptococcosis.[8] Furthermore, echinocandins are not active against *Cryptococcus* species, and echinocandin therapy makes a breakthrough cryptococcosis during echinocandin therapy possible.[1] The fact that the cell walls of zygomycetes and cryptococci lack 1,3-β-D glucan explains the poor activity of echinocandins, including caspofungin, against these fungi.[3] Malhotra et al[1] reported a patient with AIDS and Hodgkin's disease who developed *C. neoformans* pneumonia and fungemia on empiric caspofungin therapy for neutropenic fever for 2 weeks. Suzuki et al[9] also reported a case of SLE in which the patient received meropenem and micafungin as empiric therapy for fever in immunosuppressive state; unfortunately, however, this patient died of cryptococcal meningitis and pulmonary aspergillosis.

Cryptococcuria may be secondary to disseminated cryptococcosis or cryptococcemia.[4] Of the 17 patients with cryptococcuria, including our patient and the 16 patients reviewed by Kiertiburanakul et al,[4] 16 (94%) had certain underlying conditions and HIV infection was the most common disease (68%), followed by diabetic mellitus and chronic renal failure. Fourteen (82%) patients presented with cryptococcuria as a manifestation of disseminated cryptococcosis, and ten patients presented with concurrent cryptococcemia and cryptococcuria. Budding yeasts could be found in urinary analysis only in three (18%) patients. The prognosis of those with cryptococcuria was grave, with a mortality rate of 65%.

Cryptococcemia and cryptococcuria can occur not only in AIDS patients[1] but also in non-HIV infected patients with other immunocompromised conditions, such as liver cirrhosis, uremia, or SLE. The investigation of genitourinary abnormalities is necessary to check for complicated cryptococcemia.[4] Breakthrough fungal infections can occur during echinocandin targeted therapy.[1] Clinicians should be aware that the choice of antifungal agents for immunocompromised patients should also include host susceptibility as a main consideration to avoid the selection of secondary fungal pathogens.[1,9] Micafungin was not effective against *C. neoformans*, *Trichosporon*, and *Rhodotorula* species, and should be used carefully in organ failure and immunocompromised patients.[4,9,10] The finding of budding

yeasts in urinary analysis may indicate the possibility of candidiasis or cryptococcosis, and further investigation (such as urine culture) is necessary for early diagnosis and prompt therapy.

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