Fungemia and renal fungus ball formation with *Candida norvegensis* in a child with acute lymphoblastic leukemia

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Invasive fungal infections cause significant morbidity and mortality in pediatric cancer patients. Candida species are the most frequently isolated pathogen. Candida species may cause bloodstream and deep-seated infection in neutropenic children with cancer. The gastrointestinal system, lung, liver and spleen are the most frequently involved organs. Isolated renal involvement presented as abscess formation has been reported rarely in children with cancer. Herein, we report a patient with acute lymphoblastic leukemia (ALL) who presented with renal abscess and fungus ball formation due to *Candida norvegensis,* which is an unusual cause of infection.

Key words:* *acute lymphoblastic leukemia, invasive fungal infection, renal candidiasis, Candida norvegensis.

Infections cause significant morbidity and mortality in pediatric cancer patients. Approximately 20% of pediatric cancer deaths were attributed to infections[1]. It is reported that 17% of bloodstream infections in children with cancer are due to a fungal organism[1,2]. During the last years, a considerable increase in the incidence of fungal infection, from 2.9% to 7.8%, has been observed in children with cancer[3]. The mortality rate of invasive fungal infection has been reported as between 15% and 65% in different studies[3,4]. Candida species were the most frequently isolated pathogen in cancer patients with invasive fungal infection[1-4]. Candida species may cause bloodstream and deep-seated infection in neutropenic children with cancer in addition to mucosal and cutaneous infection. The gastrointestinal system, lung, liver and spleen are the most frequently involved organs[4,5]. Isolated renal involvement presented with abscess and fungal ball formation has been reported rarely in children with cancer. Herein, we report a patient with acute lymphoblastic leukemia (ALL) and candidemia who presented with renal abscess and fungus ball formation due to *Candida norvegensis*. To our knowledge, this is the first report of renal candidiasis with *C. norvegensis*.

Case Report

A two-year-old boy was admitted to our hospital with a one-week history of fever, fatigue and swelling of lymph nodes. Clinical and laboratory examination revealed the CALLA (+) pre-B cell ALL, and BFM-95 chemotherapy protocol was begun. On the 10th day of chemotherapy, he became febrile. Since he was neutropenic and had severe mucositis, empirical broad spectrum antibiotic therapy was started. Since he was still febrile on the 6th day of antibiotic treatment and culture of blood and urine remained negative, empirical fluconazole at a dose of 10 mg/kg/day was added to the treatment. Although he became well and afebrile, a low-grade fever started again after the 10th day of antibiotic treatment. *C. norvegensis* was isolated from the blood culture taken on the 6th day of fluconazole, the 12th day of antibiotic therapy. Blood cultures were processed in the mycology laboratory of our hospital by an automated blood culture system (BACTEC, Becton Dickinson). Passages to Sabouraud dextrose agar were performed. Yeast was

identified with biochemical tests using API20C AUX system (BioMérieux). Susceptibility testing was performed using the YeastOne colorimetric antifungal panel (Trek Diagnostics). The isolates were sensitive to amphotericin B (minimum inhibitory concentration [MIC]: 0.032 μg/ml), fluconazole (MIC: 16 μg/ml (S-DD), voriconazole (MIC: 0.25 μg/ml) and caspofungin (MIC: 0.5 μg/ml). The antifungal agent was changed to liposomal amphotericin B on the 16th day of the first febrile episode. Urine smear and culture were negative for fungus. High-resolution thorax tomography was normal. Abdominal ultrasonography showed bilateral grade-I increase in renal parenchymal echography and multiple hypoechogenic, well-marginated parenchymal nodules of <1 cm representing fungal abscess (Fig. 1). There were also multiple non-shadowing echogenic masses within the thick-walled cystic lesions of <2 cm located within the renal medulla. These cystic masses were in continuation with the pelvicaliceal system, representing the fungus ball formation (Fig. 2). These fungal abscesses were hyperintense on T2-weighted images and seen as hypointense masses on contrast-enhanced T1-weighted magnetic resonance images. The same organism was isolated on three repeated blood cultures taken on the 14th, 17th and 20th days of febrile neutropenia (on the 2nd and 4th days of amphotericin B treatment). In the 4th week of antifungal treatment, renal sonography demonstrated a decrease in the renal lesions and chemotherapy was started again. At two months of antifungal treatment, caspofungin was added to the therapy, since an increase in renal abscess was observed. Liposomal amphotericin B was stopped at the 3rd month, and caspofungin was continued one more month. At the 4th month of antifungal therapy, the size and number of renal lesions had clearly decreased and caspofungin was stopped. After one month, the lesions were completely resolved on ultrasonography.

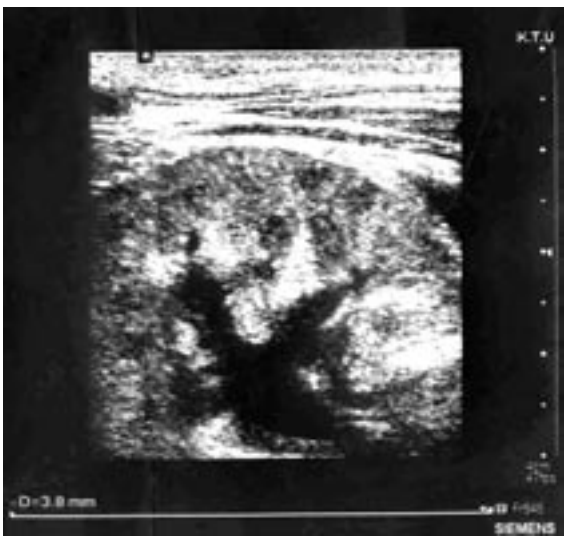

Fig. 1. Renal sonography demonstrating multiple hypoechoic parenchymal nodules.

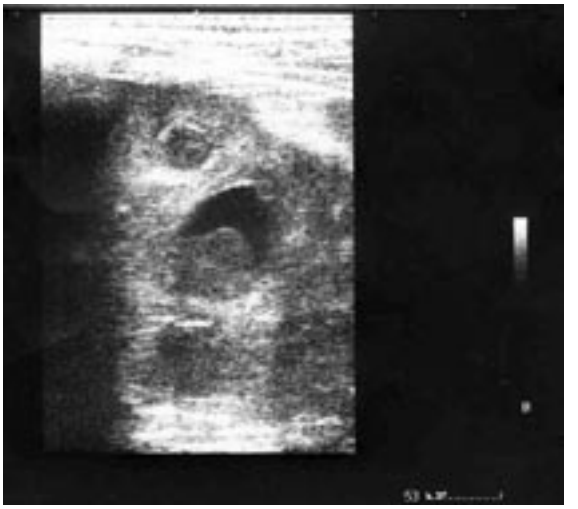

Fig. 2. Renal sonography showing non-shadowing echogenic lesions continuing with the pelvicaliceal system, representing the fungus ball.

Discussion

Invasive fungal infections are among the most lethal complications in patients being treated for cancer, and the direct cause of death in approximately 20% of cases[3-5]. Candida species account for 10% of all nosocomial bloodstream infections[1,2], and for 70% of all fungal infections in children with cancer[3]. The mortality rate of invasive candidiasis in children has been reported as 10-35%[2-4]. The spectrum of invasive candidiasis ranges from candidemia to single or disseminated organ infection with/without candidemia (to hematogenous spread of fungus to one or more organs with/without candidemia). Prolonged duration of candidemia with a central venous catheter, immunosuppression, prolonged neutropenia, prolonged antibiotic therapy, and total parenteral nutrition have

been reported as risk factors for disseminated candidiasis[4,5]. The patient described here had no permanent venous catheter, but had some other risk factors for systemic fungal infection, including underlying leukemia, neutropenia, immunosuppressive treatment, and ongoing antibacterial therapy.

Renal involvement with Candida species is usually secondary to Candida sepsis with or without involvement of other organs; however, it may be involved primarily without evidence of candidemia. The kidney may also be affected in a retrograde manner during the Candida cystitis. Renal candidiasis may present as pyelonephritis, renal abscess in parenchyma and pelvicaliceal fungus ball formation resulting in hydronephrosis. Aggregates of fragmented bits of fungi, mycelia and mucoid debris coexist freely within the renal pelvis and become molded to its contours as fungal balls[6,7]. Although there are numerous reported newborn cases with renal candidiasis presented particularly with fungus ball[7], we could find only one reported pediatric case with ALL and renal candidiasis due to *C. tropicalis*[8].

Ultrasonography is the most effective imaging modality and is positive in 96% of patients. There are no specific radiologic signs in renal candidiasis apart from fungus balls in the pelvicaliceal system or ureters, which appear as a radiolucent irregular filling defect. Sonographic appearance of renal abscess is generally as hypoechoic focal masses. On computed tomography (CT), low attenuated mass is expected. Magnetic resonance appearance of renal abscess was described as ill-defined masses with low signal intensity on T1-weighted images with increased heterogeneous signal intensity on T2-weighted images[9,10].

C. albicans accounts for 50% of Candida isolates in patients with invasive candidiasis. Among non-albicans species, *C. tropicalis*, *C. parapsilosis*, *C. glabrata* and *C. krusei* each represented 5-20% of clinical isolates, while other species such as *C. lusitaniae*, *C. guilliermondii* and *C. rugosa* are very rare[4,5]. In our case, *C. norvegensis* was isolated from four different blood cultures; therefore, renal abscess was connected to this organism. *C. norvegensis* has been an unusual cause of infections in humans[5,11]. The first clinical infection with *C. norvegensis* was described in an immunosuppressed renal transplant patient, in 1990[11]. Since then, we were able to find eight more cases that had severe underlying disease, with *C. norvegensis* infections including bloodstream infections (n: 3), peritonitis (n: 2), intraabdominal abscess (n: 1), pneumonia (n: 1), and urinary tract infection (n: 1)[12-14]. In addition to those cases, *C. norvegensis* specimens were isolated in some cases that were not pathogenically significant[11].

Renal candidiasis may be successfully treated with parenteral antifungal treatment. In the presence of urinary obstruction and renal insufficiency, percutaneous nephrostomy and irrigation with antifungal agents and/or surgical debridement in addition to systemic treatment are generally necessary[4,5,7]. In neutropenic patients, options for initial therapy of uncomplicated invasive candidiasis include liposomal amphotericin B, fluconazole and caspofungin[4,5,15]. Combination therapies of liposomal amphotericin B and caspofungin or voriconazole and caspofungin should be considered for fulminant or massive life-threatening infections, since each drug acts differently[4,5,15]. Antifungal susceptibility varies significantly among different species of *Candida*. *C. glabrata* and *C. krusei* are inherently resistant to fluconazole[4,5,15]. Although there were limited studies, it has been understood that *C. norvegensis* is also inherently resistant to fluconazole[11,14]. We thus preferred liposomal amphotericin B in our patients and later combined it with caspofungin.

In summary, we want to share our experience with this patient, since the case was interesting with respect to both the involved organ and the isolated species.

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