Candida krusei Arthritis in a Patient with Hematologic Malignancy: Successful Treatment with Voriconazole

U. Sili, M. Yılmaz, B. Ferhanoglu and A. Mert

Departments of 1Infectious Diseases and Clinical Microbiology and 2Internal Medicine, Cerrahpasa Medical Faculty, University of Istanbul, Istanbul, Turkey

Here, we report a case of disseminated Candida krusei infection in a patient who presented with arthritis. The infection was successfully treated with voriconazole after amphotericin B deoxycholate therapy had failed.

Invasive candidiasis is usually seen in special groups of patients who are immunosuppressed (e.g., they are neutropenic or are receiving steroids), have indwelling central venous catheters in place, have received broad-spectrum antibiotics, or are injection drug users [1]. Administration of fluconazole prophylaxis to patients with hematologic malignancies has substantially decreased the incidence of fungemia due to Candida albicans; however, a concomitant increase in the incidence of fungemia due to non-albicans species of Candida has been observed [2, 3]. Osteoarticular involvement is rarely encountered in patients with disseminated candidiasis [4]. Here, we report a case of disseminated Candida krusei infection in a patient who presented with arthritis. The infection was successfully treated with voriconazole after amphotericin B (AmB) deoxycholate (AmB-d) treatment had failed.

Case report. A 57-year-old man consulted our department for a swollen right knee joint. Diffuse B cell lymphoma had been diagnosed ~1 year earlier, and the patient had received radiation and chemotherapy. During his current neutropenic period, he developed pain in his right knee. Physical examination revealed that the patient was afebrile and had a tender, warm, erythematous, and swollen right knee; the patient displayed the cardinal signs of septic arthritis. Swelling progressed rapidly within a few days as the patient was recovering from neutropenia (neutrophil count increased from 100 to 1800 cells/mm³ on daily successive counts). C-reactive protein levels also increased from 30 mg/L to 130 mg/L (normal level, <5 mg/L) within 4 days.

Arthrocentesis revealed a yellow, turbid fluid with 30,000 cells/mm³, predominantly polymorphonuclear leukocytes. Gram and Ziehl-Neelsen stains were negative for microorganisms. At the time of consultation, the patient was receiving oral ciprofloxacin and fluconazole for prophylaxis. After undergoing arthrocentesis, empirical treatment with ceftriaxone and teicoplanin was started for the possibility of bacterial arthritis. However, both solid and liquid media grew yeast cells identified as C. krusei on the basis of automated pathogen identification test strip ID 32 (bioMérieux), with MICs of fluconazole and AmB of 16 µg/mL and <0.5 µg/mL, respectively (as determined by Etest [AB Biodisk]). AmB-d (1 mg/kg per day) was initiated. Hematogenous spread to the knee joint was suspected, so other organ systems were screened for evidence of candidal involvement. Urinalysis revealed fungal elements, and a urine culture revealed 6 hypoechoic solid lesions, with the largest (size, 25 × 25 mm) located in the dome of right lobe of the liver. Blood cultures continued to yield negative results, and we found no evidence of endophtalmitis, oral candidiasis, or any rash compatible with candidemia. Thus, the patient was regarded as having invasive candidiasis with articular, urinary, and hepatic involvement.

Despite receipt of AmB-d, additional arthrocenteses were performed on days 5 and 15 and revealed a leukocyte count of >10,000 cells/mm³, with a predominance of polymorphonuclear leukocytes; both joint fluid cultures were positive for C. krusei. The patient received a total dose of 1540 mg of AmB-d over a 21-day period. Because joint fluid culture continued to yield C. krusei, therapy was switched to oral voriconazole (loading dose, 400 mg administered twice; maintenance dosage, 200 mg twice per day) after voriconazole susceptibility testing was performed using the agar diffusion method (Neo-Sensitabs; Rosco Diagnostic). The leukocyte count gradually decreased to 2560 cells/mm³ (on day 6 of treatment) and 740 cells/mm³ (on day 25 of treatment), and culture results remained negative.

After 30 days of oral voriconazole treatment, lesions in the liver disappeared, and the patient was discharged from the hospital without any signs of arthritis.

Discussion. Disseminated candidiasis is usually seen in pa-
patients with hematologic malignancies who have or who are recovering from neutropenia [1]. Although *C. albicans* remains the predominant agent, candidemia due to non-*albicans* species of *Candida* have been increasing in frequency in recent years. The reason for this is probably the prophylactic use of fluconazole in neutropenic patients that has led to the emergence of strains resistant to fluconazole—in particular, strains of those species that are inherently resistant to fluconazole, such as *C. krusei* and *Candida glabrata*, and those that are genetically predisposed to develop rapid resistance, such as the new species *Candida tropicalis* [2, 3]. Our patient had disseminated candidiasis with hepatic and renal involvement that became apparent with the development of arthritis. Thus, candidal arthritis may be one of the first presenting signs of candidemia in immunocompromised patients [5].

In a recent study, the use of piperacillin-tazobactam or vancomycin rather than the use of fluconazole was found to constitute a risk for the development of *C. glabrata* or *C. krusei* candidemia [6]. In our patient, receipt of prophylaxis with piperacillin-tazobactam and fluconazole during the previous episode of febrile neutropenia may have contributed to the development of *C. krusei* fungemia.

The disseminated candidiasis with osteoarticular, hepatic, and renal involvement seen in our patient was probably due to hematogenous seeding during an episode of candidemia that most likely originated from the gastrointestinal tract. When hematogenous seeding involves joints, it usually results in monarticular arthritis affecting normal joints [7].

To the best of our knowledge, our case is the third case of *C. krusei* arthritis to be reported in the English-language literature (as determined by a search of the Medline database for articles published from 1966 to January 2007) and the first to be successfully treated with voriconazole [8–10]. Both of the other 2 patients had acute myeloid leukemia. Although one of these patients received AmB-d and had his infection resolved, the other received fluconazole but died.

Definitive information on the treatment of native joint candidal arthritis is limited [11]. Both AmB and fluconazole have been successfully used to treat infection with susceptible strains, as long as adequate drainage was provided [7, 11]. Although the *C. krusei* strain in our study was susceptible to AmB, and although drainage was provided, we could not achieve sterilization of the joint fluid in our patient. The failure of AmB to eradicate *C. krusei* may have been associated with variable levels of this drug in the joint fluid. The AmB levels in the joint fluid vary between 20% and 100% of the serum concentration [7]. Moreover, AmB was shown to have the lowest level of fungicidal activity against *C. krusei* and *Candida tropicalis*, and the slow killing rate could explain the lack of clinical response to AmB treatment for certain infections caused by these 2 species [12].

As expected, the strain was resistant to fluconazole, but it was susceptible to voriconazole, and voriconazole treatment eventually eradicated the infection, after 30 days of administration. Although we could not find any information on joint fluid concentrations of voriconazole, it has been reported that the joint fluid concentration of fluconazole approximates its plasma concentration [13].

In conclusion, *Candida* species should be considered as etiologic agents when arthritis develops in a patient with a hematologic malignancy. If *C. krusei* arthritis is refractory to AmB treatment, voriconazole may be a valuable alternative agent.

**Acknowledgments**

Potential conflicts of interest. All authors: no conflicts.

**References**