Rare Case of Septic Arthritis Caused by *Candida krusei:* Case Report and Literature Review

To the Editor:

Acute monoarthritis is a common rheumatological emergency that requires immediate investigation to rule out a possible infection. *Candida* species can be rarely isolated from joint infections[1]; however, as more aggressive strategies are used to treat patients with hematological malignancies, new pathogens have emerged[2].

We describe a 75-year-old white man with a diagnosis of acute myeloid leukemia (AML) who was admitted to the University of Texas M.D. Anderson Cancer Center with neutropenic fever and sudden onset of severe right knee pain without trauma. His history was significant for diabetes mellitus and relapsing AML refractory to treatment. At the time of admission he had been neutropenic for a year and was on his first course (day 47) of salvage therapy with fludarabine and cytarabine. He was receiving prophylaxis with fluconazole 200 mg/daily and valacyclovir 500 mg/daily for the past 4 months and levofloxacin 500 mg/daily for the past year. Antifungal prophylaxis was switched to voriconazole 200 mg twice daily, 1 month before admission, around the same time he developed right lower extremity cellulitis, treated with broad-spectrum antibiotics.

On examination, he was febrile at 38.3°C and his right knee was swollen and tender with no erythema. Passive and active range of motion was painful and limited. Initial investigations revealed serum white blood cell count 200/μl with an absolute neutrophil count 90/μl. Chest radiograph was normal and plain radiographs of the knees showed chondrocalcinosis. Differential diagnosis included septic versus crystal arthritis. Arthro-centesis of the knee yielded 60 cc of clear fluid that contained 5–10 white blood cells/high power field with no crystals. Staining of synovial fluid demonstrated no bacterial, fungal, or mycobacterial infection. The patient was then empirically treated with intravenous meropenen and daptomycin. Blood and urine cultures at admission were negative. By the fifth day, culture of the synovial fluid was positive for a yeast identified as *Candida krusei*. He was initially treated with posaconazole 400 mg twice daily orally for 10 days. He was then switched to caspofungin intravenously when symptoms did not improve. While on caspofungin he developed a bacterial bronchopneumonia and died from septic shock 21 days after starting on caspofungin.

Fungal arthritis caused by *Candida* species is uncommon. Although infrequent, *C. albicans* is the species most frequently isolated from a fungal-infected joint[1]. According to previous reports, the knees and intervertebral disks are affected more frequently. Fungal arthritis is most often due to hematogenous seeding rather than to direct inoculation of fungi, and it occurs in patients with predisposing factors[1].

Cancer patients have a higher incidence of fungemia than do noncancer patients, with leukemia patients accounting for 25% of reported cases[3]. Neutrophils are critical for protection against systemic infections and neutropenic patients have a much higher rate of visceral dissemination and death[2,3]. Since the introduction of fluconazole for fungal prophylaxis in neutropenic patients, the incidence of *C. albicans* fungemia has decreased dramatically, but has shifted toward a greater involvement of non-albicans infections over the last 2 decades[2].

C. krusei is highly vulnerable to enzymes in granules of neutrophils, thus it shows very low pathogenicity and invasiveness[4]. Its main virulence is due to a multilayered hydrophobic cell wall, which makes it easier for this fungus to adhere to and colonize inert surfaces and to develop an extensive biofilm on catheter disks[4]. Nearly 90% of the documented infections due to *C. krusei* are fungemia[4]. The most remarkable feature of *C. krusei* is its intrinsic resistance to fluconazole[2]. It remains susceptible to voriconazole, posaconazole, ravubconazole, and caspofungin. Indeed, fluconazole prophylaxis along with neutropenia and bone marrow transplant are considered specific risk factors associated with *C. krusei*[5].

In patients with high risk of invasive fungal infection, prophylaxis with voriconazole 200 mg twice daily has been shown to be as effective as prophylaxis with fluconazole 400 mg/daily in achieving fungal-free survival[2].

Our patient represents the sixth case of fungal arthritis caused by *C. krusei* that has been reported in the last 30 years. These include a case of a heroin addict[6] and 5 cases of patients with hematologic malignancies[7,8,9,10] (Table 1). All 5 patients with hematologic malignancies were neutropenic and 3 of them had been receiving fluconazole at the time of the diagnosis of fungal arthritis. The *C. krusei* isolated from our patient was sensitive to voriconazole *in vitro*. This case may represent a failure of prophylaxis, which cautions against the false sense of assurance when the patient is receiving appropriate prophylaxis in a neutropenic state. However, our patient developed cellulitis of the same limb at the time of the switch of fluconazole to voriconazole. The cellulitis on the same limb may have served

Table 1. Reported cases of *Candida krusei* arthritis.

	Case 1[6]	Case 2[7]	Case 3[8]	Case 4[9]	Case 5[10]	Present Case
Year published	1982	1987	2006	2007	2007	2011
Age, yrs	18	41	62	79	57	75
Sex	M	M	M	M	M	M
Underlying disease	Drug addiction	AML	AML	AML	Lymphoma*	AML
Neutropenic	No	Yes	Yes	Yes	Yes	Yes
Fever	No	Yes	Yes	Yes	No	Yes
Arthritis	Left knee	Right knee	Spondylodiscitis	Right knee	Right knee	Right knee
Synovial fluid	Turbid	Serous	NA	Serous	Turbid	Serous
Macroscopic quantity, cc	NA	10	NA	NA	NA	60
WBC	4.4×10^9/l	2.8×10^9/l	NA	1.9×10^9/l	30×10^9/l	5–10/hpf
Positive sample culture	Synovial liquid	Sputum and synovial liquid	CT-guided fine-needle biopsy	Synovial liquid	Synovial liquid and urine	Synovial liquid
C krusei treatment	Clotrimazole	Amphotericin B	Amphotericin B + caspofungin + voriconazole	NA	Amphotericin B followed by voriconazole	Posaconazole followed by caspofungin
Infection outcome	Cured	Cured	Cured	Death	Cured	Death††
Devices	No	CVC	CVC	No	NA	CVC
Previous antibiotic	No	No	Yes	Yes	Yes	Yes
Antifungal prophylaxis	No	No	Fluconazole	Fluconazole†	Fluconazole	Voriconazole

AML: acute myelogenous leukemia; WBC: white blood cell count; NA: not available; CVC: central venous catheter. * Diffuse B cell lymphoma. † Patient was receiving treatment with fluconazole because of *C. tropicalis* arthritis. *C. krusei* was isolated in subsequent arthrocentesis. †† Bacterial infection.

as the port of entry. It is likely that he became infected with this organism at this time, before he had achieved full, steady, effective levels of voriconazole. Once *C. krusei* colonized the joint, it may have been more difficult to achieve the levels needed to suppress the infection in the synovial fluid. A case report of voriconazole levels in synovial fluid in humans showed them to be lower than serum levels[11]. In addition, with the lack of neutrophils, the host was unable to clear the fungal infection.

In general, in a patient with intact host immunity, most septic arthritis is bacterial and is generally treated with appropriate antibiotics alone. The therapeutic responses are excellent if the infection is diagnosed early. Our patient, however, was neutropenic and immunocompromised, and had prior antibacterial and antifungal prophylaxis, all risk factors for opportunistic infections. Empiric therapy in susceptible hosts presenting with acute monoarthritis should include not only antibacterial, but also antifungal agents effective for emerging non-*C. albican* species like the one isolated in our case. Finally, a delay in clinical response may require switching or adding therapies, particularly if there is uncertainty about the levels attained by specific antiinfective agents in the joint.

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