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Case Report

Candida Glabrata Arthritis: Case Report and Review of the Literature of Candida Arthritis

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Abstract: We report a case of arthritis due to *Candida (Torulopsis) glabrata* in two different joints at different times in the same patient. The first episode of arthritis was situated in the right ankle and lasted more than 1 year before the patient agreed to the proposed treatment. Therapy with intravenous amphotericin B and oral fluconazole failed. A cure was achieved with weekly intra-articular administration of amphotericin B, which was continued for more than 20 weeks and combined with oral itraconazole. Several weeks later the patient developed *Candida glabrata* arthritis of the left knee while still taking itraconazole. Immediately, intravenous amphotericin B therapy was started and was successful. Because there were no previous invasive point manipulations or trauma, the infections were considered to be haematogenously disseminated. Chronic corticosteroid and repeated antibiotic therapy for infectious exacerbations of chronic obstructive pulmonary disease and alcohol abuse are the presumed risk factors in this otherwise immunocompetent patient.

Keywords: Candida arthritis; Septic arthritis; *Torulopsis glabrata*

Introduction

Osteoarticular infections with *Candida glabrata* are extremely rare. In the literature, seven cases of vertebral osteomyelitis (reviewed in [1,2]), one of hyoid osteomyelitis [3] and one of prosthetic hip joint infection [4] caused by *C. glabrata* have been described. Treatment of the prosthetic joint infection consisted of removal of the prosthesis and local irrigation with amphotericin B. We report the case of a patient who had two independent episodes of peripheral *C. glabrata* arthritis in two different joints.

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Case Report

A 40-year-old man with a medical history of alcohol abuse, gout and corticoid-dependent chronic obstructive pulmonary disease (COPD) with emphysema developed a painful swelling of the right ankle during treatment with intravenous broad-spectrum antibiotics, methylprednisolone up to 120 mg/day and classic inhalational therapy for an infectious COPD exacerbation. There were no previous invasive joint manipulations, trauma or a history of intravenous drug abuse.

Cultures of the aspiration fluid of the right tibio-talar joint were positive for *C. glabrata*. Because the patient refused further hospitalisation and intravenous amphotericin B treatment, oral fluconazole 200 mg twice daily was prescribed, but the drug was taken sporadically.

One year later he consulted the Department of Rheumatology because of increasing pain at the right ankle. The joint was swollen and tender, and mobility was reduced. The synovial fluid contained 13 000 leucocytes/μl with 75% neutrophils and 25% lymphocytes; polarisation microscopy revealed no crystals. Synovial fluid and biopsy cultures were still positive for *C. glabrata*, susceptible to amphotericin B and flucytosine and resistant to fluconazole on a mycogram. The routine laboratory tests showed a normal erythrocyte sedimentation rate (ESR), an elevated C-reactive protein

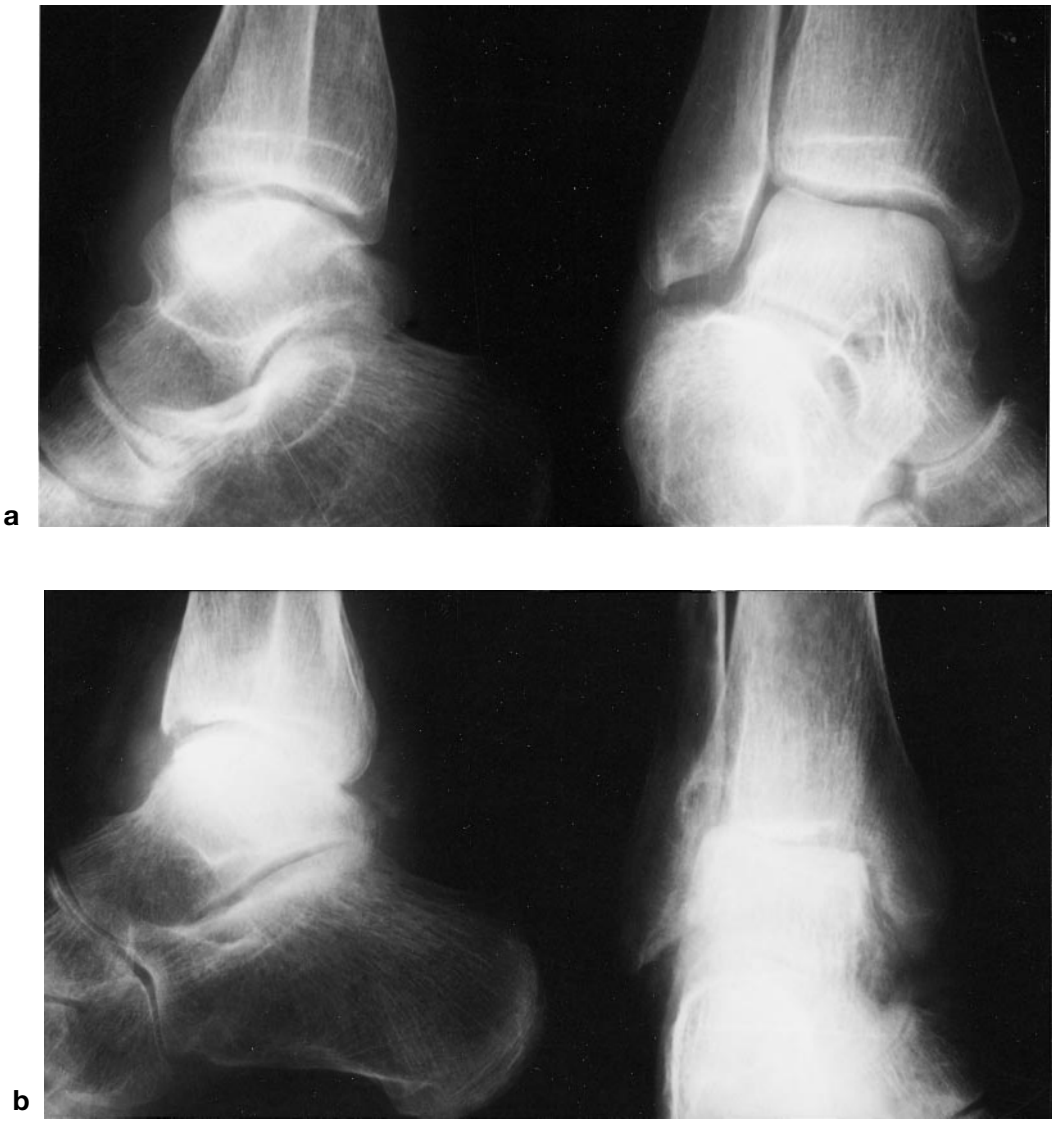

Fig. 1. Anterior-posterior and lateral radiographs of the right ankle (**a**) at the onset of the first symptoms and (**b**) 2 years later.

(CRP) of 6.8 mg/dl, 11 500 white blood cells (WBC)/μl, normal renal function and liver tests, and uric acid of 5.5 mg/dl. The values of immunoglobulins, complement, CD4, CD8 and CD20 positive lymphocytes were normal. HIV tests were negative but a tuberculin skin test was positive. Radiographs of the ankle (Fig. 1) showed arthritic destruction, and $^{99}Tc^{m}$-MDP bone scintigraphy and leucocyte scintigraphy were strongly positive. Screening for a possible source of the *C. glabrata* arthritis, including repeated blood, urine and sputum cultures, repeated echocardiography, abdominal ultrasound and leucocyte scintigraphy, was negative. Screening for active tuberculosis was also negative. Radiographs of the chest showed a picture of emphysematic COPD but no infiltrates.

Intravenous amphotericin B up to 1 mg/kg/day and fluconazole 400 mg/day were given. Repeated arthrocentesis and joint lavage with 0.9% saline solution were performed. Amphotericin B had to be stopped at a total dose of 1200 mg because of renal failure and anorexia. The treatment failed and the cultures remained positive. After switching to intra-articular administration of amphotericin B 50 mg weekly and oral itraconazole 2 $\times$ 200 mg/day, the swelling of the ankle disappeared and the cultures became sterile. The intra-articular application of amphotericin B was continued for more than 20 weeks. About 2 months later the patient developed *C. glabrata* arthritis of the left knee, while still taking itraconazole. Again no source of infection was found. Intravenous amphotericin B was restarted and a cumulative dose of 1300 mg was tolerated. This therapy was now successful and the knee returned to normal function. The arthritis did not relapse in either joint.

Discussion

Candida arthritis is uncommon. The incidence is unknown but seems to increase following an increase of other serious *Candida* infections. In intravenous drug abusers, *Candida* has been noted as the causative agent in septic arthritis at rates of up to 20% [5]. The great majority of *Candida* arthritis is caused by *C. albicans*, followed by *C. tropicalis* [6–8]. Of the other non-albicans species, next to the isolated case of *C. glabrata* [4], *C. parapsilosis* [9,10], *C. krusei* [11], *C. guilliermondii* [12] and *C. zeylanoides* [13] have been found in septic joints [14,15].

Two clinical patterns of fungal arthritis are observed: an acute-onset type with synovial and systemic symptoms and usually an early diagnosis; and a mild chronic-course type with little pain and few articular and systemic symptoms, leading to a diagnostic delay that can last for several years [14,15]. As well as arthritis, isolated cases of *Candida* bursitis have also been described [6,16].

As in other types of septic arthritis, three different ways of *Candida* joint infection have been distinguished: direct inoculation by injection or trauma, inoculation by surgery and arthritis secondary to haematogenous dissemination, which is the most frequent [15]. Although in the described case *C. glabrata* was never demonstrated in blood cultures, the infection must have been disseminated haematogenously on both occasions, considering the absence of invasive joint manipulations. In hospitalised children less than 6 months of age with underlying diseases, which have an elevated risk for haematogenously originated *Candida* arthritis, arthritis is frequently polyarticular and often accompanied by metaphyseal osteomyelitis. In older children and adults, monoarticular involvement of the larger joints predominates and the arthritis is usually a complication of disseminated candidiasis [7,14,15]. In intravenous drug addicts a predilection for fibrocartilagenous joints such as costochondrial joints, intervertebral discs and sacro-iliacal joints, has been noted [5,15,17].

The increase of disseminated candidiasis over the past few years has been ascribed to acquired or induced immunodeficiency or suppression, intravenous drug abuse, long-term antibiotic therapy, intravascular access, parenteral nutrition and other invasive procedures [18–20]. In our patient, alcohol abuse and long-term antibiotic and corticoid therapy were the risk factors and because there were no central venous catheters nor intravenous drug abuse, the comprised lungs or the odontal region, which was in a very poor state, might have been the entrance point for the infection [21–24].

C. albicans remains the most common pathogen in yeast infections but since the widespread use of fluconazole, a shift has been observed to other *Candida* species, of which *C. tropicalis*, *C. parapsilosis*, *C. glabrata*, *C. guilliermondii* and *C. krusei* are the most important [18,20,25,26]. It is likely that *Candida* osteoarticular infections also follow this shift.

In *Candida* arthritis, amphotericin B, alone or in combination with flucytosine, is still the standard antibiotic treatment. Following the guidelines for acute haematogenously disseminated metastatic *Candida* infection, amphotericin B 0.5–1 mg/kg/day is given intravenously over 28 days [27]. Other authors mention doses up to 1.3 mg/kg/day [28] and total doses up to 3 g [7], but the optimal total dose and treatment duration have not been established. Flucytosine 100–150 mg/kg/day is given orally in four divided doses [27]. The use of flucytosine alone is not recommended because of development of resistance during therapy. The duration of treatment with azole drugs should be at least 6 weeks [28] but the optimal duration has not been established. A serious problem of intravenous amphotericin B is its toxicity, while resistance to it is still infrequent in the various *Candida* species with the exception of *C. lusitaniae*, in which resistance is constitutional [29,30].

Antifungal azole drugs are widely used in systemic mycosis but their role in osteoarticular infections remains to be established, although there are increasingly reports of their success. The limited number of cases makes it difficult to carry out controlled studies.

The reported case shows the efficacy of intravenous amphotericin B in the early joint infection, its limitations due to toxicity and its failure in the chronic joint infection. Because there was no evidence of non-compliance with the therapy since hospitalisation in the rheumatology department, it is assumed that the used azole drugs failed, reflecting the elevated resistance patterns of *C. glabrata* to the used azole drugs. Intra-articular amphotericin B in doses of 5–25 mg per injection or irrigation, mostly given as additional therapy to systemic treatment, was considered to be useful in other cases of *Candida* joint infection [4,14,31,32]. Failure was described for the administration of 8 mg in toto, divided into single doses of 1–2 mg over 12 days in a patient with *C. parapsilosis* knee joint arthritis [9]. In chronic yeast infection limited to the joint, intra-articular amphotericin B could be considered in the face of unacceptable toxicity or side-effects of intravenous amphotericin B, or as an addition to enteral or parenteral therapy.

Next to antifungal drug therapy and repeated arthrocentesis, mainly in chronic *Candida* arthritis, surgical joint drainage or débridement can be necessary. An infected prosthetic joint only exceptionally will be cured without removal of the prosthesis [14,15,33,34].

As with other antibiotic therapy, treatment with antifungal drugs should be based on the different à priori susceptibility of the different species and, if possible, on in-vitro susceptibility testing [35,36]. However, mycograms are not perfect predictors of in-vivo susceptibility and outcome. The different test systems show discrepancies of in-vitro susceptibility, and successful treatment of *Candida* infections has been reported with drugs that were found to be resistant in vitro [35]. Because fungi can be missed in classic bacterial cultures, specific fungal cultures should be carried out whenever fungal infection is suspected. The

joint levels produced by systemic application of fluconazole and flucytosine are comparable to the serum levels [8,37,38]; those of amphotericin B vary, but usually reach sufficient concentrations [14].

In conclusion, in *Candida* arthritis, if the standard antibiotic treatment with intravenous amphotericin B cannot be followed or fails, the choice of other drugs should be based on the susceptibility profile of the causative species. Intra-articular amphotericin B application may have a place in the management of confined infection and surgery should be considered in unfavourable courses.

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