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Review

Bilateral polymicrobial osteomyelitis with *Candida tropicalis* and *Candida krusei*: a case report and an updated literature review

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SUMMARY

Objectives: We present a case of bilateral polymicrobial osteomyelitis with *Candida tropicalis* and *Candida krusei*, and review the literature on Candida osteomyelitis.
Methods: PubMed was searched for cases of Candida osteomyelitis published in the English-language literature between 1970 and 2010.
Case: A 60-year-old previously healthy man was hospitalized with gallstone pancreatitis. Between 3 weeks and 6 months after hospitalization, he developed bilateral osteomyelitis of the feet with *C. tropicalis* and *C. krusei*. The patient was treated with surgery, fluconazole, and a liposomal formulation of amphotericin B. The left lower limb was amputated, and at a 2-year follow-up, the patient had almost no pain in his right foot.
Literature review: We identified 40 new cases in the literature since the latest review in 2004. Most cases of Candida osteomyelitis are caused by *Candida albicans*, but an increasing number are caused by non-albicans species. The prognosis is favorable, with full recovery in the majority of cases.
Conclusions: Candida osteomyelitis should be considered when a patient presents with risk factors and pain without previous trauma, because Candida, despite being part of the normal flora, is the fourth leading cause of hematogenous nosocomial infections. The recommended treatment is surgery and fluconazole as monotherapy or initially combined with a fungicidal agent, either a different amphotericin B formulation or an echinocandin.

1. Introduction

Osteomyelitis occurs acutely or chronically and may be caused by hematogenous spread or direct inoculation.[1,2] The infection can be caused by a low pathogenic microorganism, and the clinical symptoms may be sparse, making early diagnosis difficult.[3,4] Osteomyelitis caused by Candida is rare. However, an increase in predisposing risk factors, such as broad-spectrum antibiotics, central venous catheters (CVC), parenteral nutrition, and immunosuppression have been identified in recent decades, and more cases are expected.[3,5,6] Arias reviewed 110 case reports of Candida osteomyelitis published between 1970 and 2002.[5] The most frequent localizations were the vertebra (40%) and sternum (8%). The most common associated species was *Candida albicans*, followed by *Candida tropicalis* and *Candida glabrata*. To our knowledge, six cases have been described in which polymicrobial osteomyelitis was caused by two or more species of Candida.[7–12] We identified only two cases of *Candida krusei* osteomyelitis.[7,13]

We present a case in which a previously healthy patient with gallstone pancreatitis developed bilateral polymicrobial osteomyelitis of the feet caused by *C. tropicalis*, *C. krusei*, and *Eikenella corrodens*. We further review and update the English-language literature of cases of Candida osteomyelitis.

2. Methods

We conducted a PubMed search of the English-language literature published between 1970 and 2010, applying the following free-text words: osteomyelitis, osteitis, Candida, multifocal, polymicrobial, and multi-species. Subsequently, Candida was individually combined with the free-text words using 'AND'. We further reassessed all cases included in the review by Arias et al.[5] covering the period from 1970 to 2002 and reviewed all identified articles presented in that review. Furthermore, all identified reported cases of microbiologically verified Candida osteomyelitis from the period 2002 to 2010 were reviewed.

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3. Case presentation

A healthy 60-year-old man was hospitalized in February 2007 (day 1) with gallstone pancreatitis and was prescribed penicillin (2 000 000 IU × 3 intravenous (IV)), metronidazole (500 mg × 3 IV), and gentamicin (240 mg × 1 IV). On day 2, the antibiotics were replaced with cefuroxime (1.5 g × 3 IV).

On day 21, the patient developed pain in his left ankle, bilateral swelling of his feet and ankles, and leukocytoclastic vasculitis, verified by a punch biopsy. The patient was prescribed oral prednisolone (25 mg/day), which diminished the skin lesions. Cefuroxime was suspected to be the cause of the vasculitis and was replaced by the same antibiotics as above. However, the patient's ankle pain remained unchanged.

On day 34, blood cultures tested positive for non-albicans Candida, and fluconazole (400 mg/day IV) and voriconazole (320 mg/day IV) were prescribed. On day 41, cultures revealed *C. tropicalis*, and the azoles were substituted by a liposomal formulation of amphotericin B (LF AmB) for 14 days (160 mg × 1 IV). The minimum inhibitory concentration (MIC; by E-test) was 2.0 μg/ml for fluconazole and 0.5 μg/ml for amphotericin B. There were no signs of ocular candidiasis or endocarditis. A continually elevated C-reactive protein (CRP) of 168 mg/l and a white blood cell count (WBC) of 17×10^9/l on day 48 led to the puncture of a pancreatic cyst; the culture tested positive for *C. tropicalis*.

The patient's clinical condition normalized, and on day 55 he was discharged with decreasing swelling and pain in his left ankle.

On day 72, the patient was readmitted to the hospital with symptoms and clinical signs of septic arthritis in the left ankle joint and pus exuding from the left heel. From days 72 to 91, the patient's left ankle was treated surgically three times. The first time, an arthroscopic synovectomy was also performed. None of the surgeons found any evidence of osteomyelitis. The patient was treated with vancomycin IV and dicloxacillin IV based on tissue culture results that were positive for streptococci, *Staphylococcus aureus*, and coagulase-negative staphylococci. X-rays showed no evidence of osteomyelitis, but the patient still had an elevated CRP of 86 mg/l and a WBC count of 12×10^9/l.

On day 112, a leukocyte scan revealed increased uptake in the left calcaneus stretching up the back of the lower leg, a small increase in uptake in the right tuber calcaneus, and a smaller charge proximally around the triceps surae muscle.

On day 125, a surgical revision of the left ankle was performed. Necrotic soft tissue was removed, but no signs of bone or joint involvement were found. On day 138, a surgical revision of the left ankle revealed a necrotic calcaneus. The talus was partially corroded. The right foot was not revised because there were no symptoms or objective findings. Based on the tissue culture from the calcaneus, which was positive for *E. corrodens*, the patient received penicillin (2 000 000 IU × 4 IV). On day 149, another surgical revision was performed. Tissue culture from the necrotic calcaneus tested positive for *C. tropicalis*. The MICs for *C. tropicalis* were determined to be 0.5 μg/ml for fluconazole and 0.25 μg/ml for AmB. Fluconazole (400 mg/day IV) was instituted.

On day 163, the patient had a high crural amputation. On day 178, after 14 days of fluconazole treatment and 35 days of penicillin treatment, the antibiotics were discontinued because the cultures were negative, and the patient was discharged for outpatient monitoring.

Six months after the primary gallstone pancreatitis, on day 185, the patient had pain and a purulent discharge from the right heel and was readmitted to hospital. A surgical revision of the heel revealed an abscess and a necrotic calcaneus. The patient was administered cefuroxime (1.5 g × 3 IV). On day 189, the samples from the calcaneus tested positive for Candida. Cefuroxime was substituted by fluconazole (400 mg × 1 IV) for 14 days until day 203, when the final culture was positive for *C. krusei* and *C. tropicalis*, and the patient received LF AmB (180 mg × 1 IV). The MICs for *C. krusei* were determined to be 256 μg/ml for fluconazole and 0.004 μg/ml for AmB. The MICs for *C. tropicalis* were determined to be 1.0 μg/ml for fluconazole and 0.047 μg/ml for AmB.

On day 271, a magnetic resonance imaging (MRI) scan showed osteomyelitis of the calcaneus, talus, distal fibula, medial cuneiform bone, and metatarsals I, III, IV, and V. On day 277, a follow-up biopsy of the calcaneus tested positive for coagulase-negative staphylococci, but not for Candida; therefore, rifampin (300 mg × 2 IV) and fusidic acid (500 mg × 3 IV) were initiated.

On day 320, after 4 months of treatment with LF AmB, the patient was discharged to outpatient monitoring. On discharge, the CRP was 34 mg/l and the WBC count was 11×10^9/l.

The 6-month control leukocyte scan continued to show a slightly increased uptake in the right calcaneus, but no clinical signs of infection. At 12 months and 24 months, the follow-up MRIs showed unchanged conditions. The patient had no objective signs of infection and almost no pain.

4. Literature review

From the literature published between 2002 and 2010, we identified 40 new cases in addition to the case described above (Table 1).[1,5,13–39] A total of 21 cases (51%) were caused by *C. albicans* and 14 (34%) by non-albicans species, including *C. tropicalis*, *Candida parapsilosis*, *Candida dubliniensis*, *C. krusei*, and *C. glabrata*. Eleven of the 41 patients were female, and four of the patients were children. Of the known predisposing risk factors, previous or current antibiotic usage was the most common. Additional risk factors were diabetes, CVCs, previous surgery, IV drug abuse, and general immunosuppression. The most frequent localization was the spine (27 cases; 66%). Other locations included the tibia, femur, sacrum, costae, metatarsals, talus, calcaneus, and humerus. Seven patients had current or previous candidemia. The predominant symptom was persistent pain. In some cases, the patients had a fever. Treatment included a combination of surgery and pharmacological treatment. In 11 cases, the treatment was solely pharmacological. The treatment period varied from 14 days preoperatively to lifelong therapy in one case. Fluconazole was the most common agent used. Treatment with caspofungin and LF AmB were used to good effect. There were only two reported cases of adverse reactions to treatment; in one case this resulted in the treatment being switched from amphotericin B deoxycholate and AmB to LF AmB because of elevated transaminases and nephrotoxicity. In 80% (33 patients) of the cases, there was full recovery, with three patients having complete clinical remission but with sequelae visible by MRI. One patient died from lung cancer 1 month after the diagnosis of osteomyelitis, and another patient died 11 days after the diagnosis of osteomyelitis because of chronic nephropathy. Three cases were reported but not described, and three patients had less pain after treatment, but not complete remission.

In Arias et al., 61 cases (58%) were caused by *C. albicans*, 17 (16%) by *C. tropicalis*, and seven (7%) by *C. glabrata* (see Appendix).[5] Other species were *Candida lusitaniae*, *Candida paratropicalis, Candida pseudotropicalis, C. parapsilosis, Candida holmii, C. krusei*, and *Candida guilliermondii*. A total of 60 cases (57%) were localized to the spine. The second most frequent localization was the sternum, in 21 (20%) cases. Other localizations included the facial bones and long bones, with a few cases in the bones of the foot and hand.

The treatment administered was fluconazole, AmB, or a combination. Ketoconazole, itraconazole, fluconazole, and AmB have each been combined with flucytosine and miconazole have been combined with AmB. A total of 66 patients (62%) made a