CASE REPORT AND LITERATURE REVIEW / OLGU SUNUMU VE LİTERATÜR DERLEMESİ

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Osteoarticular *Candida* Infection: Report of Three Cases and Literature Review of 44 Patients

Osteoartiküler Kandida Enfeksiyonu: Üç Olgu Sunumu ve 44 Hastalık Literatür Derlemesi

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Abstract

Fungal infections in the bones and joints are rare. *Candida* spp. osteomyelitis is also a very rare entity. The most common pathogen is *Candida albicans*, but an increase in the incidence of non-albicans *Candida* osteomyelitis has been reported in recent years. Herein, we present three patients with non-*albicans Candida* osteomyelitis. Osteoarticular involvement occurred in the lumbar vertebrae in one patient, in the hand in one patient, and the foot in the other patient. Diabetes mellitus and long-term antibiotic use were common risk factors in all three cases. In the patient with vertebral osteomyelitis, surgical intervention and foreign body were other risk factors. Magnetic resonance imaging was used in the diagnosis and the pathogens were isolated from deep tissue cultures. Surgical debridement was performed in all cases and antifungal treatment was given for 6-24 weeks. There was no reinfection or relapse during clinical and radiological follow-up. The patient with osteomyelitis of the foot died due to to acute cerebrovascular disease. In our study, the literature review for publications related to osteoarticular Candida infection was made between April 2010 and June 2019 and 44 cases are reviewed. Our aim in this study was to draw attention to *Candida* osteoarticular infections and to emphasize the importance of targeted treatment by defining the pathogen.
Keywords: Spondylodiscitis, fluconazole, caspofungin, systematic review, liposomal amphotericin b

Öz

Funguslara bağlı kemik eklem enfeksiyonları nadirdir. Kandida türlerine bağlı osteomiyelit de oldukça nadir görülen bir durumdur. Etken olarak en sık *Candida albicans* görülür, ancak son yıllarda non-albicans *Candida*'ların da osteomiyelitlerde sıklığının arttığı bildirilmektedir. Bu yazıda non-*albicans Candida* osteomiyeliti olan üç olgu sunuldu. Osteoartiküler tutuluma bakıldığında olguların birinde lomber vertebra, birinde el, diğerinde ise ayak osteomiyeliti vardı. Olguların üçünde diabetes mellitus ve uzun süreli antibiyotik kullanımı ortak risk faktörleriydi. Vertebral osteomiyelit olan olguda ayrıca cerrahi girişim ve yabancı cisim varlığı diğer risk faktörleriydi. Olguların tanısında manyetik rezonans görüntüleme kullanıldı ve alınan derin doku kültüründe etken izole edildi. Tüm olgulara cerrahi debritman yapılarak altı hafta ile 24 hafta arasında değişen sürede antifungal tedavi verildi. Olgularda klinik ve radyolojik takiplerde enfeksiyon tekrarlamadı. Ayağında osteomiyeliti olan olgu akut serebrovasküler hastalık nedeni ile eksitus oldu. Çalışmamızda Nisan 2010-Haziran 2019 tarihleri arasında osteoartiküler Candida enfeksiyonu ile ilgili literatür taraması yapıldı ve 44 olgu derlendi. Çalışmamızda bu olguları sunmadaki amacımız, kandidaya bağlı osteoartiküler enfeksiyonlara dikkati çekmek ve etken tanımlanmasıyla hedefe yönelik tedavinin önemini vurgulamaktır.
Anahtar Kelimeler: Spondilodiskit, flukonazol, kaspofungin, sistematik derleme, lipozomal amfoterisin b

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Introduction

Fungal infections of the bone and joints are rare. *Candida* osteomyelitis is also a very rare entity[1,2]. Although it usually occurs via hematogenous dissemination, it may also develop as a result of direct inoculation or contiguous spread[2-6]. Vertebrae are commonly involved in adults, though other osseous structures may also be affected[1,7,8]. Clinical findings and radiological imaging are nonspecific in *Candida* infections[3,6].

Although *Candida albicans* seems to be the most common agent, non-albicans *Candida* species have also been increasingly reported in cases of osteomyelitis in recent years[7,9,10]. Current guidelines state that successful outcomes can be achieved with surgical treatment and long-term antifungal therapy (at least six months)[3,7,11]. Indications for surgical treatment include development of neurological deficit, spinal instability, presence of large abscess, and symptom exacerbation or lack of improvement during medical treatment[3,7,12,13].

Especially in patients who do not respond to long-term antibacterial treatment, osteoarticular *Candida* infections may develop in different anatomical locations depending on the underlying diseases. Performing deep tissue culture (DTC) in such cases is important to document the causative agent and plan treatment.

Herein, we aimed to bring attention to the possibility that *Candida* may be the cause of osteoarticular infections and to evaluate the characteristics of similar cases in the literature.

Case Reports

Case 1

A 50-year-old male with a 10-year history of diabetes mellitus (DM) reported intermittent antibiotic use (drug unknown) for the last three months due to soft tissue infection secondary to trauma to the fourth finger of his left hand. However, the problem continued despite antibiotics. He presented to our outpatient clinic with swelling, pain, and a non-healing, exudative wound in his finger. Physical examination revealed an open fibrinous wound 1 cm in diameter, on the dorsal surface of the left fourth finger at the level of the distal interphalangeal joint. There was also a necrotic wound with a base 1.5 cm in diameter and purulent discharge on the ulnar side of the finger where the joint structure was visible.

Laboratory results showed glycated hemoglobin (HbA1c): 12.2% (4.5-6), C-reactive protein (CRP): 0.04 mg/dl (<0.5), erythrocyte sedimentation rate (ESR): 6 mm/h (0-20), white blood cell (WBC) count: 9.62x10^3/µL (4.8-10.8). Magnetic resonance imaging (MRI) and DTC were scheduled and the patient was hospitalized in the Endocrinology Department with a diagnosis of uncontrolled DM. Magnetic resonance imaging revealed a 13x13 mm collection with skin fistulization and peripheral enhancement consistent with abscess at the level of the left hand interphalangeal joint of the fourth phalanx. Findings consistent with osteomyelitis and septic arthritis were also detected in medial and distal sections of the fourth phalanx (Figure 1A). The abscess was drained, deep tissue biopsy was obtained, and the sample was sent to the central microbiology laboratory for DTC. *Candida parapsilosis* was isolated in culture. The causative agent was identified at the species level using *matrix-assisted laser desorption ionization-time of flight mass spectrometry* (MALDI-TOF MS) (Bruker Daltonics, Germany). Antifungal susceptibility testing was performed using Sensititre YeastOne™ (TREK Diagnostic System, East Grinstead, UK). This system did not indicate the relevant minimum inhibitory concentration (MIC) values. Intravenous (IV) fluconazole (FLC) 800 mg once daily was initiated after Infectious Diseases consultation. The patient underwent debridement and amputation of the fourth finger at the proximal interphalangeal joint in the Orthopedics Department on day 7 of treatment. The amputated finger was sent to the pathology laboratory. Changes compatible with inflammation, necrosis, ulceration, and osteomyelitis were observed on pathological examination. Two weeks after the amputation, the patient's treatment was adjusted to FLC 400 mg per oral (PO) twice daily and he was discharged for outpatient follow-up. However, he stated that he no longer wished to continue treatment. When he came to the outpatient clinic for his follow-up visit, he reported that he discontinued the drug therapy after using it for a total of six weeks. On physical examination, the patient's stump appeared clean. Laboratory tests indicated HbA1c: 5.5% (4.5-6), CRP: 0.07 mg/dl (<0.5), and WBC: 7.69x10^3/µl (4.8-10.8). No lesions were detected on follow-up MRI (Figure 1B); therefore, the patient was considered to be cured and treatment was discontinued. He had no active symptoms or pathological findings on repeated MRI in two outpatient follow-up visits after treatment cessation, and follow-up was discontinued after two months.

Case 2

A 61-year-old male with a 2-year history of DM had undergone surgery one year earlier due to lumbar disc hernia. He was diagnosed with L2/3 paravertebral abscess and spondylodiscitis that was considered to be a postoperative device-related complication. He had used teicoplanin 400 mg intramuscular (IM) and rifampicin 900 mg PO once daily for three months. The patient had no test results related to the diagnosis he had received at the other center. The patient's back pain had persisted and he was able to walk only with support. Upon treatment cessation, he experienced fever, weight loss, exacerbation of back and leg pain, and substantial mobility limitation, and was admitted to the Neurosurgery Department of our hospital.

On physical examination, he exhibited 2/5 bilateral strength loss in the lower extremities. In laboratory tests, hemoglobin: 10.8 g/dl (12-17), ESR: 68 mm/h (0-20), CRP: 6.39 mg/dl (<0.5), HbA1c: 6.7% (4.5-6), and other results were within physiological limits. On MRI, osteitis and discitis were detected in the L2/L3 bodies, and an abscess formation up to 8 mm thickness was detected in the paravertebral area at the level of the L2 body. Surgery was planned based on these findings. The patient's screw caps and rod were removed, the abscess was drained, and a culture sample was collected and sent to the Central Microbiology Laboratory. Histopathological examination was not performed. Gram staining of the abscess sample revealed yeast, upon which the patient was started on liposomal amphotericin B (AMP-B) 3 mg/kg IV once daily and transferred to the Infectious Diseases Clinic. Abscess culture yielded *Candida tropicalis*. The agent was identified at the species level using MALDI-TOF MS (Bruker Daltonics, Germany). Antifungal susceptibility testing was performed using Sensititre YeastOne™ (TREK Diagnostic System, East Grinstead, UK). This system did not indicate the relevant minimum MIC values. Magnetic resonance imaging performed after one month of treatment showed spondylodiscitis and intradiscal abscess at the L2/L3 level and osteomyelitis inferior to the L1 vertebra (Figure 2). An interventional radiologist drained the abscess again. No growth was detected in repeat abscess culture. The patient received IV AMP-B for a total of three months after the second drainage, after which his treatment was changed to FLC 400 mg PO twice daily with outpatient follow-up. At the end of treatment, laboratory tests showed CRP: 0.78 mg/dl (<0.5), WBC: 7.49x10^3/µL (4.8-10.8), and ESR: 43 mm/h (0-20). Antifungal treatment was discontinued at six months, while the patient continued physical therapy due to bilateral 1/6 strength loss in his lower extremities. Follow-up was discontinued because the patient decided to continue his physical therapy in his city of residence.

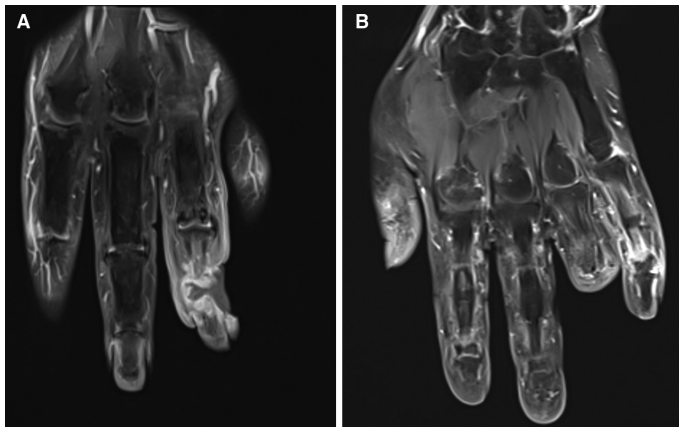


Figure 1. A) Magnetic resonance imaging (MRI) of the left hand before treatment. Fat-suppressed T1-weighted contrast-enhanced MR image of the fourth finger of the left hand shows deformation and loss of integrity in the osseous structure of the medial and distal phalanges, contrast enhancement in the medullar osseous structure and soft tissue, a 13x13 mm abscess formation (white arrow) with fistulization to the skin and peripheral contrast enhancement at the interphalangeal joint. B) MRI of the left hand after treatment. Fat-suppressed T1-weighted MRI acquired six months after amputation of the medial and distal phalanges of the left fourth finger shows no pathological contrast enhancement in the proximal phalanx or cutaneous and subcutaneous soft tissue of the fourth finger

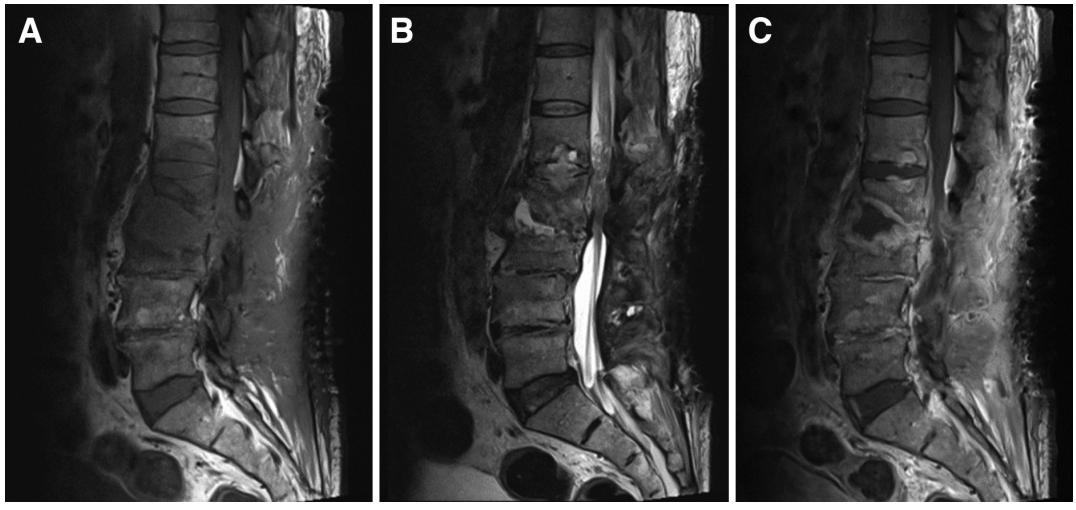


Figure 2. Lumbar magnetic resonance imaging (MRI) before treatment. T1-weighted (A), T2-weighted (B), and contrast-enhanced T1-weighted (C) MRI images showed. Findings compatible with spondylodiscitis in intervertebral disc and discovertebral joint at the L2-3 vertebral level that was hypointense in T1-weighted, hyperintense in T2-weighted cross-sections, and had heterogeneous contrast enhancement in contrast-enhanced T1-weighted images. Intradiscal abscess formation with peripheral contrast enhancement was also detected in the intradiscal space. Contrast enhancement and thickening of the anterior epidural soft tissue consistent with phlegmon were detected at the L1, L2, and L3 vertebra levels, as well as contrast enhancement in the anterior paravertebral soft tissue and paraspinal muscles consistent with inflammation

Case 3

A 70-year-old female with a 20-year history of DM presented to our outpatient clinic. She explained that she had developed multiple wounds in both feet during a stay in intensive care unit for urosepsis four months earlier. The patient received local treatment and care after discharge and applied to us upon worsening of her wounds.

On physical examination, her temperature was 38.1 °C and other vital signs were stable. There was a 5-cm open fibrinous wound on the dorsal surface of the right foot, a 7-cm open fibrinous wound on the dorsal surface of the left foot, and a 4-cm necrotic area on the medial surface of the left first toe. No pathologies were detected in other physical examination. The patient had a Foley's catheter and her urine was cloudy. Laboratory tests showed HbA1c: 7.6% (4.5-6), CRP: 4.9 mg/dl (<0.5), ESR: 89 mm/h (0-20), and creatinine: 2.08 mg/dl (0.51-0.95). Direct microscopy and Gram staining of urine samples revealed leukocytes but no microorganisms. Other findings were within physiological limits. Both feet were biopsied and the samples were sent to the central microbiology laboratory for DTC. Bilateral foot MRI was performed. Magnetic resonance imaging revealed increased contrast enhancement in the cutaneous and subcutaneous tissue and muscles at the tarsal-metatarsal joints of both ankles that was interpreted as cellulitis and myositis (Figure 3). Empirical ertapenem 500 mg IV once daily was initiated. ESBL-positive *E. coli* was isolated in urinary culture. *Candida metapsilosis* was isolated in DTC from both feet. Caspofungin (CAS) 50 mg IV once daily was added to the ertapenem therapy. In the third week of antifungal treatment, the patient underwent surgical procedure in the plastic surgery department. To avoid osteomyelitis, the necrotic tissues in both feet were debrided and the first and second toes of the left foot were amputated at the metatarsophalangeal joint and the interphalangeal joint, respectively. Signs of ischemia and necrosis were detected on histopathological examination of the excised material. *C. metapsilosis* and *Stenotrophomonas maltophilia* were detected in culture of the material collected intraoperatively. The agent was identified at the species level using MALDI-TOF MS (Bruker Daltonics, Germany). Antifungal susceptibility testing was performed using Sensititre YeastOne™ (TREK Diagnostic System, East Grinstead, UK). This system did not indicate the relevant minimum MIC values. Ertapenem was discontinued, and IV trimethoprim/sulfamethoxazole (TMP/SMX) 3x160/800 mg was initiated. After being treated with CAS for six weeks and TMP/SMX for two weeks, the patient was discharged with a prescription for FLC 400 mg PO once daily. Two months after discharge and while still under treatment, she was admitted to the neurology intensive care unit due to acute cerebrovascular disease and died.

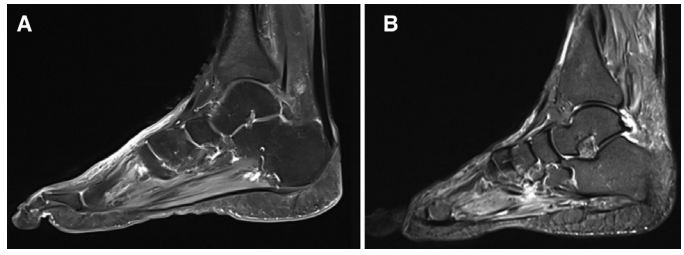
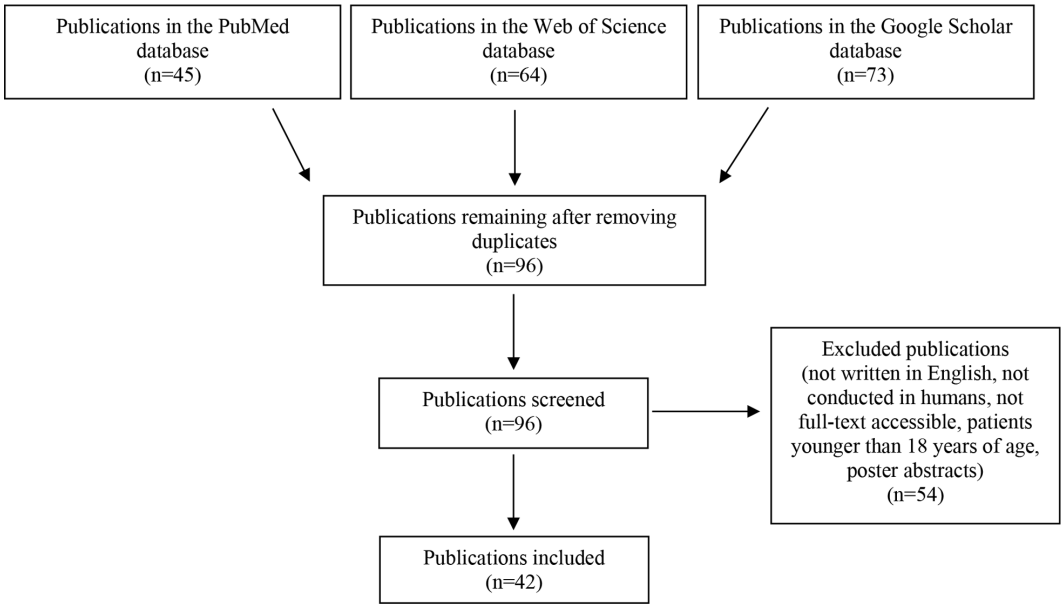


Figure 3. Bilateral foot magnetic resonance imaging (MRI) before treatment. Right (A) and left (B) foot MRI STIR images showed markedly increased signal intensity in the dorsal surface of the metatarsal area and in cutaneous/subcutaneous soft tissue and muscle structures that suggested cellulitis and myositis



Algorithm 1. Flow chart showing the number of publications screened and included in the study

Literature Review

We performed a review of relevant studies published between April 2010 and June 2019. The literature search was performed in the PubMed, Google Scholar, and Web of Science databases using the keywords "Candida osteomyelitis", "*Candida* arthritis", and "*Candida* spondylodiscitis". Limiting the search to studies with accessible full text, written in English, and conducted in humans yielded 42 publications[4,5,9,10,14-51].

A summary of these studies is shown in Algorithm 1 and Table 1. Of the 44 cases described in the articles, 29 (66%) of the patients were male and 15 (34%) were female. The mean age was 53.1±17.7 years. *C. albicans* was isolated in 22 cases (48%), non-albicans *Candida* species were isolated in 23 cases (50%), and *Candida* was not subtyped in one (2%) of the cases. The most common risk factor was history of surgery, which was present in 16 (36%) of the cases. The most common osteoarticular system involvement was vertebral, reported in 18 cases (41%). The most frequently used antifungal agents were azoles (25 cases, 57%), echinocandins (10 cases, 23%), polyenes (eight cases, 18%), and combination therapy in one case (2%). Thirty-seven (84%) of the patients recovered and four (9%) died.

Discussion

Although rare, *Candida* species may infect the osteoarticular system and lead to osteomyelitis[1]. While the most common causative agent is *C. albicans*, non-albicans *Candida* species have also been increasingly reported in osteomyelitis cases in recent years[7,9,52]. According to our literature review, the frequency of *C. albicans* was 48% while non-albicans *Candida* rate was 50% (Table 1). In one study, the most common causative agents in *Candida* osteomyelitis were *C. albicans* (69%), *C. tropicalis* (15%), and *C. glabrata* (8%)[11]. However, two retrospective studies showed that non-albicans *Candida* are becoming increasingly common in *Candida* osteomyelitis and can cause mixed infections with bacteria, especially *Staphylococcus aureus*[7,9]. non-albicans *Candida* species were isolated in all three of our patients. The isolated agents are similar to those isolated in recent years. In this study, we identified the causative agent at the species level using MALDI-TOF MS and performed antifungal susceptibility testing using Sensititre YeastOne™. Treatment was adjusted according to the results of antifungal sensitivity tests.

Candida osteomyelitis has a subacute or chronic course[7,53]. In adults, the vertebrae are the most commonly affected osteoarticular component, with the lumbar region frequently involved. In vertebral involvement, *Candida* is usually located in the center of the intervertebral disc, causing narrowing of the disc cartilage. This results in damage and destruction of the vertebral end plates and underlying vertebral bone[2,5,14]. That injury leads to further disease progression and destruction if *Candida* osteomyelitis is left untreated[36]. Authors have emphasized that *Candida* species must be considered in osteoarticular infections that do not respond to prolonged antibacterial therapy, especially in patients with risk factors for *Candida* infection[52]. One of our patients had lumbar vertebral osteomyelitis, one had osteomyelitis of the hand, and the other had osteomyelitis of the foot. However, there were no signs of bone destruction. All three patients presented with abscesses.

Risk factors for *Candida* osteomyelitis are central venous catheters, immunosuppression, IM drug use, DM, surgery, and antibiotic use[14,54-56]. *Candida* biofilms also play an important role in the development of prosthetic joint infection. Most *C. albicans* infections are associated with the formation of biofilm in the host or on the surfaces of medical devices and prostheses[57]. DM and long-term antibiotic use were common risk factors in all three of our cases. Although biofilm presence could not be demonstrated in the patient with vertebral osteomyelitis, he had previous surgical intervention and presence of foreign body as other risk factors. Moreover, in addition to the other risk factors, Case 3 also history of treatment in an intensive care unit.

Laboratory tests are not specific for the diagnosis of fungal osteomyelitis. For instance, the inflammattory biomarkers ESR and CRP usually increase slightly[4,14,37]. In a study of 207 fungal osteomyelitis patients, ESR was elevated in 87% of the patients[1]. Alkaline phosphatase level may increase in some patients[2]. Blood and urine culture are rarely positive[5]. Therefore, clinical and standard laboratory parameters may not be sufficient for the diagnosis of *Candida* osteomyelitis. Compatible with the literature, Cases 2 and 3 in our study had elevated ESR and CRP while levels in Case 1 were within physiological limits. When osteomyelitis is suspected, MRI is more frequently preferred for early diagnosis as it is more sensitive and specific than tomography[6,58,59]. Lifeso[60] reported that MRI was 96% sensitive and 92% specific in their study. Torres-Ramos et al.[2] reported that MRI was more specific and sensitive, and effectively demonstrated the presence of epidural and paraspinal infection. In all three of our cases, MRI was used as a diagnostic imaging method and revealed abscess formations.

The most important method for the definitive diagnosis of infectious diseases is isolation of the causative agent. For the definitive microbiological diagnosis of *Candida* vertebral osteomyelitis, a biopsy sample must be cultured and the treatment must be determined based on the biopsy and/or culture result[2,27,61]. The need for biopsy and culture for accurate diagnosis and treatment has also been emphasized in the literature[7,9]. As fungal osteomyelitis requires very different treatment, it is crucial to identify the microorganism[61]. Miller and Mejicano[1] suggested that if the first biopsy culture is

Table 1. Literature review of *Candida* osteomyelitis cases

Authors	Year	Number of cases	Sex/age (years)	Anatomic location	Causative agent	Risk factors	Treatment	Outcome
Cho et al.[14]	2010	1	Female/70	Vertebral	*C. parapsilosis*	Surgery	FLC	Recovery
Dailey and Young[15]	2011	1	Male/69	Vertebral	*C. glabrata*	Antibiotic use	AMP-B	Recovery
Burton et al.[16]	2011	1	Male/72	Vertebral	*C. parapsilosis*	DM, surgery	FLC	Recovery
Sung and Chun[17]	2011	1	Female/63	Ankle	*C. parapsilosis*	DM, HT	AMP-B	Recovery
Lu et al.[18]	2012	1	Male/75	Knee	*C. krusei*	DM, AML	POS→CAS	Death
Lim et al.[19]	2012	1	Male/73	Shoulder	*C. parapsilosis*	-	FLC	Under follow-up
Yuste et al.[20]	2012	1	Female/42	Iliac bone	*C. albicans*	Surgery	FLC	Recovery
Grimes et al.[21]	2012	1	Female/63	Vertebral	*C. albicans*	Surgery	FLC	Under follow-up
Fleming et al.[22]	2012	1	Female/65	Foot	*C. albicans*	Surgery	FLC	Recovery
Kumar et al.[23]	2012	1	Female/27	Knee	*C. tropicalis*	-	AMP-B→FLC	Recovery
Joshi[24]	2012	1	Male/63	Vertebral	*C. albicans*	CKD, HCV, alcohol use	FLC	Recovery
Kelesidis and Tsiodras[25]	2012	1	Male/41	Vertebral	*C. albicans*	HIV	CAS	Recovery
Springer and Chatterjee[26]	2012	1	Female/65	Shoulder	*C. albicans*	DM, rheumatoid arthritis	MICA→ FLC	Recovery
Kaldau et al.[9]	2012	1	Male/60	Ankle	*C. tropicalis* *C. krusei*	Antibiotic use, immunosuppression	Liposomal AMP-B	Recovery
Bali et al.[27]	2013	1	Male/55	Maxilla	*C. albicans*	-	FLC	Re-infection
Chen et al.[28]	2013	1	Male/41	Vertebral	*C. albicans*	IV drug use	FLC	Recovery
Marupudi et al.[29]	2013	1	Male/74	Vertebral	*C. albicans*	DM, surgery	FLC	Recovery
Prevost and English[30]	2013	1	Male/62	Rib	*C. albicans* *C. parapsilosis*	Surgery	FLC	Recovery
Eves et al.[31]	2013	1	Male/73	Rib	*Candida* spp.	Surgery	FLC	Recovery
Savall et al.[32]	2013	1	Male/22	Vertebral	*C. albicans*	Surgery	FLC	Recovery
Imamura et al.[33]	2014	1	Female/45	Elbow	*C. albicans*	SLE	FLC	Recovery
Tan et al.[34]	2014	1	Male/47	Vertebral	*C. glabrata*	Immunosuppression, testicular seminoma, psoriatric arthritis	CAS→POS	Recovery
Taneja et al.[35]	2014	1	Male/68	Hip	*C. albicans*	CKD, Crohn's disease, immunosuppression	FLC	Death
Brembilla et al.[5]	2014	1	Male/27	Vertebral	*C. albicans*	Surgery	FLC	Recovery
Lopez et al.[10]	2014	1	Male/51	Thumb	*C. parapsilosis*	Surgery	CAS→FLC	Recovery
Toki et al.[36]	2014	1	Female/54	Finger	*C. glabrata*	Trauma, antibiotic use	ITR→FLC→FLS	Recovery
Oksi et al.[37]	2014	1	Male/37	Vertebral	*C. dubliniensis*	IV drug use	Liposomal AMP-B → FLC	Recovery
Kulcheski et al.[38]	2015	1	Male/39	Vertebral	*C. albicans*	Antibiotic use, trauma, alcoholism	FLC	Recovery
Magano et al.[39]	2015	1	Male/36	Rib, costochondral joint	*C. albicans*	Surgery, antibiotic use	CAS	Recovery

Table 1. Continued

Authors	Year	Number of cases	Sex/age (years)	Anatomic location	Causative agent	Risk factors	Treatment	Outcome
Oichi et al.[40]	2015	1	Male/79	Vertebral	*C. tropicalis*	Immunosuppression, CHF	MICA→ FLC	Recovery
Gopinathan et al.[4]	2016	2	Female/19 Male/64	Vertebral Vertebral	*C. tropicalis* *C. tropicalis*	CKD, immunosuppression DM, CKD	AMP-B→FLC FLC	Recovery No follow-up
Jones et al.[41]	2016	1	Female/25	Hip	*C. albicans*	Immunosuppression	FLC	Recovery
Gamarra-Hilburn et al.[42]	2016	1	Female/68	Elbow	*C. parapsilosis*	Rheumatoid arthritis	CAS→ FLC	Recovery
Çevik et al.[43]	2016	1	Male/35	Knee	*C. albicans*	Surgery	AMP-B	Recovery
Ma et al.[44]	2016	1	Male/52	Vertebral	*C. tropicalis*	Acute myeloid leukemia, immunosuppression	MICA	Recovery
Iacuzzo and Monticelli[45]	2017	1	Male/86	Pubis	*C. albicans*	-	FLC	Recovery
Nahra et al.[46]	2017	1	Female/31	Sacrum	*C. albicans*	-	MICA→FLK	Recovery
Yingling et al.[47]	2017	1	Female	Ankle	*C. parapsilosis*	CKD, HIV, dementia, antibiotic use	FLC→CAS was added	Death
Attie et al.[48]	2018	2	Male/40 Male/45	Mandible Mandible	*C. albicans* *C. albicans*	IV drug use, surgery IV drug use, surgery	FLC FLC	Recovery Recovery
Gagliano et al.[49]	2018	1	Male/66	Vertebral	*C. glabrata*	DM, spondyloarthrosis, HCV	AND	Recovery
Heath et al.[50]	2019	1	Male/65	Sternum	*C. auris*	COPD, CKD, surgery	POS	Death
Kaushal et al.[51]	2019	1	Female/29	Maxillofacial	*C. tropicalis*	Palatal ulcer	AMP-B	Recovery

FLC: Fluconazole, AMP-B: Amphotericin B, CAS: Capsofungin, FLS: Flucytosine, VOR: Voriconazole, MICA: Micafungin, ITR: Itraconazole, POS: Posaconazole, AND: Anidulafungin, COPD: Chronic obstructive pulmonary disease, CKD: Chronic kidney disease, HCV: Hepatitis C virus, HT: Hypertension, AML: Acute myeloid leukaemia, SLE: Systemic lupus erythematosus, CHF: Chronic heart failure, DM: Diabetes mellitus

negative, a second biopsy should be performed only if there is high probability of fungal osteomyelitis. If the second biopsy is also negative, surgical biopsy and culture are recommended. Deep tissue culture was performed in all of our three cases and yielded non-albicans *Candida* growth in all three cases. We were able to identify the causative agent with the first DTC in all of our cases.

Medical therapy together with surgical treatment when needed are essential components in the treatment of osteoarticular infections[1,3,4]. FLC and echinocandins are commonly used antifungal therapies in osteoarticular *Candida* infections (Table 1). The use of FLC was especially predominant until the introduction of polyenes[1]. Osseous tissue concentrations of FLC are approximately 33% in human studies and 100% in animal studies. It was also reported that AMP-B has good osseous tissue penetration, but there are insufficient data on echinocandins[62]. Eltoukhy and Crank[63] reported that FLC and AMP-B had sufficient penetration into osseous tissue, whereas echinocandins, posaconazole (POS), voriconazole (VOR), and itraconazole (ITR) did not.

FLC or AMP-B was the first choice for osteoarticular joint infections[according to the Infectious Diseases Society of America (IDSA) 2009 treatment guidelines for candidiasis[64]. The 2016 update of that guideline recommends FLC and echinocandins as strong recommendation, low evidence based on recent case series demonstrating their superiority to AMP-B[3]. However, data on the use of echinocandins in the treatment of *Candida* osteomyelitis are limited[11]. While antifungal treatments are given systemically, agents such as AMP-B deoxylate or FLC can be administered intraosseously; however, this practice is controversial[5,65,66]. Recovery rates increase substantially when antifungal treatment is continued for at least six months[3,7,11].

Surgical debridement is frequently performed in combination with antifungal treatment in *Candida* osteomyelitis[4,52,67]. In vertebral osteomyelitis, surgical treatment is especially

indicated for patients who developed neurological deficit under medical treatment and for patients with vertebral instability, large abscesses, or worsening symptoms[7,13,14,38]. In the IDSA 2016 revised candidiasis management guidelines, surgical treatment is recommended for selected patients as strong recommendation, low evidence[3]. In previous studies, a combination of surgery and antifungal therapy was used in 57% of the patients and the reported success rate was 88%[9,11]. Combined antifungal and surgical treatment was used in all three of our cases. One patient was treated with FLC, one with AMP-B, and the other with CAS. Oral FLC was used as maintenance therapy in two patients. The duration of antifungal therapy in our patients varied between six and 24 weeks. As studies have been based on case reports and case series, there is no clear recommendation on treatment duration, although the 2016 IDSA guidelines emphasize that favorable outcomes can be attained with six months of antifungal therapy[3]. In a 2014 study evaluating 23 cases, antifungal therapy was reported to be successful when used for a mean duration of 45 days (38-83 days) in combination with surgery[68]. In our first patient, the total treatment duration together with amputation was six weeks.

Conclusion

Candida osteomyelitis must be kept in mind in osteoarticular infections in patients who have risk factors and/or are unresponsive to long-term antibiotic therapy. Since early diagnosis and treatment are important for mortality and morbidity, special attention must be paid to identifying the causative agent, planning targeted therapy, and regular follow up of the patient.

Ethics

Ethics Committee Approval: Ethics committee approval was not received for this retrospective study.

Informed Consent: Informed consent was not obtained for this retrospective study.

Peer-review: Externally and internally peer-reviewed.

Authorship Contributions

Surgical and Medical Practices: F.A., N.N.A., Concept: F.A., N.N.A., Design: F.A., N.N.A., Data Collection or Processing: E.Ç., M.K., Ş.O., E.Ö., İ.T., F.A., Analysis or Interpretation: F.A., N.N.A., İ.K., Literature Search: F.A., N.N.A., G.Y., Writing: F.A.

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