



Case report

Diagnosis and treatment for primary *Candida parapsilosis* infection of the native knee joint: A case report

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ABSTRACT

Introduction and importance: Candida arthritis is a very rare disease and *Candida parapsilosis* infection of the native knee joint is extremely rare. It is challenging to diagnose and treat because the clinical manifestations, laboratory and radiologic findings are not specific and not well defined. We report the rare case of *C. parapsilosis* infection of the native knee joint.

Case presentation: A 67-year-old man visit outpatient clinic for persistent right knee pain and effusion. Inflammatory markers were elevated and the biochemical studies of joint fluid showed elevated WBC counts. Under assumption of septic arthritis, arthroscopic irrigation and debridement were performed. *C. parapsilosis* was isolated on intraoperative knee joint culture. Fluconazole was used under diagnosis of Candida arthritis. Once there were no relapse of infection, total knee arthroplasty was implemented.

Clinical discussion: As Candida arthritis can be lead to poor prognosis, Candida arthritis should be considered in patients with untreated knee infections. Blood and radiographic examination, and fungus culture from the knee joint should be accompanied for early diagnosis. Total knee arthroplasty may be considered after treatment of Candida infection with fluconazole. Prognosis was similar compared with patients who underwent total knee arthroplasty for primary knee osteoarthritis.

Conclusion: If patients complaint persistent knee pain with or without effusion, surgeons should consider the possibility of Candida infection. After diagnosis of Candida arthritis, proper antifungal agents should be used for treatment of infection. After the infection has cleared up, total knee arthroplasty can be planned.

1. Introduction

Candida arthritis is a very rare disease and Candida infection of the native knee joint is extremely rare. And, most of the cases were associated with immunosuppressive conditions such as cancer, HIV, chronic steroid use, cancer, and recreational drugs [1,2]. It is challenging to diagnose and treat because the clinical manifestations, laboratory and radiologic findings are not specific and not well defined [3]. There are several studies about Candida infection after total knee arthroplasty [3], but studies of the native knee joint infections are rarely reported. We report on a case that showed good clinical results by performing total knee arthroplasty after treatment with an antifungal agent for *C. parapsilosis* of the native knee joint. The work has been reported in line with the SCARE criteria [4].

2. Case presentation

A 67-year-old man who had medical history of hypertension visited our outpatient clinic for right knee pain for over 2 months without any injury. He had no history of autoimmune disease, HIV, cancer, chronic steroid use, recreational drug use, smoking and drinking. In the initial X-ray, the patient showed early osteoarthritic change of the knee joint (Fig. 1A). The patient took medication under diagnosis for degenerative osteoarthritis of right knee. A year after first outpatient visit, he visited our hospital for acute right knee pain with knee joint effusion and erythema. He had no other symptoms of systemic infection or fever prior to the hospital visit. From the date of the first outpatient visit, the patient had no history of intra-articular injection or other procedure. Compared with the X-ray taken 1 year ago, osteoarthritic change was advanced (Fig. 1B). Blood tests and joint fluid analysis were performed to differentiate the knee joint infection. Blood tests showed elevated ESR (23 mm/h, reference range < 20 mm/h), CRP (2.85 mg/dl, reference range

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<0.0– 0.5 mg/dl). About 70 cc of right knee joint aspiration was done and joint fluid was yellowish and turbid. The biochemical studies of joint fluid were as follows: WBC 247200 (neutrophil 90% mononuclear cell 10%). The gram stain, AFB stain and fungus culture of the joint fluid showed negative results. Knee joint infection could be diagnosed by considering blood test and the biochemical studies of joint fluid. Under the assumption of knee joint infection, arthroscopic irrigation and synovectomy were performed by knee surgeon with over 10 years of experience. *C. parapsilosis* was isolated on intraoperative knee joint culture (Fig. 1C). Intravenous fluconazole 400 mg was injected daily for 4 weeks and then usage of oral fluconazole 400 mg was planned for 6 months. After arthroscopy, joint aspiration was performed once a month for 4 months. In fungus culture of right knee joint, *C. parapsilosis* was cultured in the first 2 months but in the next 2 months, *C. parapsilosis* was no longer cultured. 6 months after arthroscopy, the patient visited outpatient clinic with persistent right knee pain. MRI study showed synovial enhancement with bone destruction of right proximal tibia that could suggest osteomyelitis (Fig. 1D). On suspicion of osteomyelitis, oral fluconazole was taken for additional 6 months. A year after discontinuation of fluconazole, the patient continued to complain of right knee

pain, but there were no signs of infection considering the blood test including inflammatory marker such as ESR, CRP and negative results of fungus culture of the knee joint. Compared with the previous X-ray, osteoarthritic change was significantly advanced so total knee arthroplasty was planned (Fig. 1E). Total knee arthroplasty progressed similarly to patients who underwent total knee arthroplasty for primary osteoarthritis and intraoperative fungus culture came out negative. 43 months after total knee arthroplasty the patient had no evidence of infection and Oxford knee score was 42, which showed good clinical outcome [5]. Prognosis was similar compared with patients who underwent total knee arthroplasty for primary knee osteoarthritis (Fig. 1F).

3. Discussion

Candidiasis is uncommon in immunocompetent patients. Previously, many lines of evidence have indicated that most patients with fungal infection are immunosuppressed with predisposing factors. For example, candidiasis is associated with autoimmune disease, HIV, chronic steroid use, cancer cachexia, and recreational drugs [1,2]. Healthy hosts can also develop fungal musculoskeletal infections from

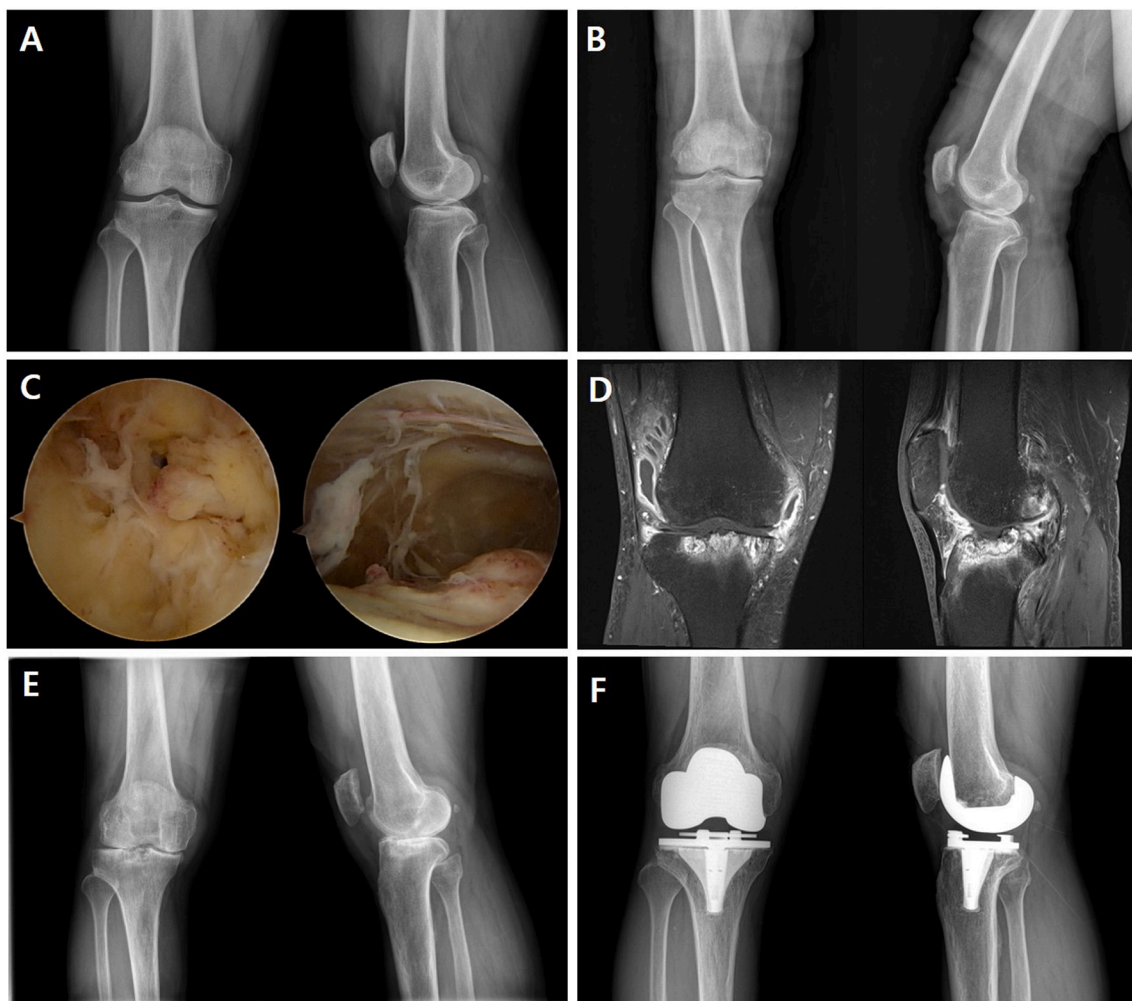


Fig. 1. A 67-year-old man with *Candida* arthritis of the right knee due to *Candida parapsilosis*.

A Initial X-ray of right knee showed early osteoarthritic change.

B X-ray of the right knee on a year follow up showed progression of degenerative osteoarthritis without bone destruction.

C Under arthroscopy, inflammatory synovium was observed.

D MRI T2-weighted image 6 months after arthroscopy demonstrated progressed osteoarthritic change and bone destruction of right proximal tibia that could suggest osteomyelitis.

E X-ray after 22 months after arthroscopy showed progressed osteoarthritic change and bone destruction.

F X-ray of right knee joint 43 months after total knee arthroplasty.

nosocomial exposures, such as prior surgery or placement of indwelling foreign bodies. Fungal infections can be introduced via direct implantation, as seen in the intravenous drug use community, in trauma victims, and as a complication of parenteral treatment [3,6]. The apparent pathogenesis of most cases of *Candida* arthritis is that of hematogenous dissemination to the joint. The mammalian synovium is extremely vascular and contains no limiting basement membrane, promoting easy access of blood contents to the synovial space. Therefore, hematogenous seeding of *Candida* may affect normal joints [7]. However, direct inoculation and contiguous spread of infection also occur. Infection can also be introduced at the time of surgery. Given the delayed onset of infection in many cases, taking a careful history of prior procedures, including intra-articular injections, and penetrating trauma to the site of infection, can help establish a route of direct inoculation [8,9]. In our clinical experience, there was no predisposing factor for *Candida* infection, no knee procedure, or no trauma history. There were no systemic symptoms and the blood culture result was negative. We could consider the diagnosis of primary *Candida* infection in the native knee joint.

C. parapsilosis is an opportunistic human pathogenic fungal species and also an uncommon cause of septic arthritis [3]. The most common fungal group causing osteoarticular infection, the *Candida*, comprises at least 15 distinct species, of which *C. albicans* is by far the most common. As immunosuppression and antifungal exposure increase, the incidence of infections caused by non-*albicans* *Candida* species increases [9]. In recent years, there has been an increasing number of *C. parapsilosis* infections reported, with their pathogenesis associated with many factors, including adhesion, biofilm formation, and hydrolytic enzymes [10,11]. However, reports of primary *C. parapsilosis* infection in native knee joints are very rare [12].

Septic arthritis or tuberculosis was initially suspected, and *Candida* was not considered as a cause because it is rarely reported in an immunocompetent patient; however, postoperative infectious arthritis caused by bacteria or tuberculosis is not rare in an immunocompetent patient [2]. The data suggested that local pain and swelling were the most common clinical manifestations of *C. parapsilosis* infection, while fever and erythema occurred infrequently. Since the symptoms are always mild and unspecific, the diagnosis can often be delayed.

Owing to their rarity and generally subacute presentation, the most important aspect of the diagnosis of these infections is their inclusion in the differential diagnosis, particularly in immunocompetent patients. We initially suspected septic arthritis, and arthroscopic irrigation and debridement were planned and implemented. Fortunately, we were routinely performing intraoperative fungus culture, and the results of intraoperative culture showed *C. parapsilosis* and we were able to start antifungal agent. As the clinical manifestations and inflammatory markers are not specific for *Candida* arthritis, arthrocentesis or arthroscopy is warranted for the definitive diagnosis [13,14].

The most common radiological abnormalities in *Candida* arthritis were bone destruction and joint effusion, followed by extension into soft tissues, decrease of articular space, osteoarthritis and periosteal reaction, and/or synovitis [15]. However, these findings are not exclusive to *Candida* arthritis.

Recent literature favors the use of fluconazole or an echinocandin over Amphotericin B [16]. Peter et al. strongly recommended Fluconazole, 400 mg (6 mg/kg) daily, for 6–12 months or an echinocandin (casposfungin 50–70 mg daily, micafungin 100 mg daily, or anidulafungin 100 mg daily) for at least 2 weeks followed by fluconazole, 400 mg (6 mg/kg) daily, for 6–12 months in *Candida* osteomyelitis. On the other hand, in the case of *Candida* septic arthritis, they recommend using fluconazole alone for 6 weeks or echinocandin for 2 weeks followed by fluconazole for 4 weeks [8]. Recently, fluconazole is supposed to be superior to echinocandin for the treatment of *C. parapsilosis* arthritis on the basis of the decreased in vitro activity of echinocandin against *C. parapsilosis* and reports of echinocandin resistance among selected isolates [17]. The optimal duration of antifungal therapy remains to be defined with individual considerations of immune

impairments, type of joint, and adequacy of debridement. The patient in this case complained of continuous effusion and bone destruction was progressing on MRI and X-ray findings taken 6 months after administration. Accordingly, fluconazole was used for 12 months under the diagnosis of *Candida* osteomyelitis.

Adequate and/or repeated drainage is often critical to successful therapy. Involvement of a prosthetic joint with *Candida* arthritis requires resection arthroplasty [18]. Some authors strongly recommend surgical drainage in all cases of *Candida* septic arthritis [8]. The rationale for medical therapy alone versus combined medical and surgical intervention in individual cases was not apparent in most reports. There are few reports that good results were obtained only with medical treatment [15]. Therefore, more research will be required on which patients can be administered medical therapy without surgical treatment.

A new prosthesis may be inserted after successful clearance of the local infection as defined by lack of return of symptoms after cessation of therapy [19]. In our clinical experience, there was no recurrence or specific symptoms for 1 year after discontinuation of fluconazole and the inflammatory marker continued to be normal, and the culture result was negative, therefore a total knee arthroplasty was implemented.

4. Conclusion

We report the case of *Candida* arthritis developing in native knee joint without predisposing factors. If patients complaint persistent knee pain with or without effusion, surgeons also should consider the possibility of *Candida* infection in the differential diagnosis. In addition to detailed blood examination and radiographic examination, it is worth to consider fungus culture under assumption of *Candida* infection. After the diagnosis of *Candida* arthritis, proper antifungal agents should be used for treatment of infection. Arthroscopic irrigation and debridement are helpful in the treatment of infection. After there is no relapse of infection, total knee arthroplasty can be implemented and good clinical results can be expected. Although clinically good result was obtained in this case, it is considered that further studies are needed due to the limitations of the short follow-up period and insufficient cases.

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Ethical approval

This is a case report study, no ethical approval was needed. On the other hand, the patient had been informed and gave their consent regarding this publication.

Consent

Written informed consent was obtained from the patient for publication of this case report and accompanying images. A copy of the written consent is available for review by the Editor-in-Chief of this journal on request.

Registration of research studies

This manuscript is not a human study, but a case report.

Guarantor

Jae Hwi Han

CRediT authorship contribution statement

JH Han performed the operation and perioperative management of

the patient. JH Han also acquired and collected the data and drafted the manuscript. JH Yoo participated in the operation, perioperative management of the patient. S Choi revision of the manuscript.

Declaration of competing interest

None.

References

- [1] U. Sili, M. Yilmaz, B. Ferhanoglu, A. Mert, Candida krusei arthritis in a patient with hematologic malignancy: successful treatment with voriconazole, *Clin. Infect. Dis.* 45 (2007) 897–898, <https://doi.org/10.1086/521253>.
- [2] L. Legout, M. Assal, P. Rohner, D. Lew, L. Bernard, P. Hoffmeyer, Successful treatment of Candida parapsilosis (fluconazole-resistant) osteomyelitis with caspofungin in a HIV patient, *Scand. J. Infect. Dis.* 38 (2006) 728–730, <https://doi.org/10.1080/00365540500447192>.
- [3] Hang Fang, Lisi Huang, Rongkai Zhang, Denghui Xie, Hengbiao Sun, Chun Zeng, et al., Recurrent arthritis caused by Candida parapsilosis: a case report and literature review, *BMC Infect. Dis.* 19 (2019) 631, <https://doi.org/10.1186/s12879-019-4255-1>.
- [4] R.A. Agha, T. Franchi, C. Sohrabi, G. Mathew, for the SCARE Group, The SCARE 2020 guideline: updating consensus Surgical CAse REport (SCARE) guidelines, *International Journal of Surgery* 84 (2020) 226–230, <https://doi.org/10.1016/j.ijso.2020.10.034>.
- [5] D.W. Murray, R. Fitzpatrick, K. Rogers, H. Pandit, D.J. Beard, A.J. Carr, et al., The use of the Oxford and knee scores, *J Bone Joint Surg Br.* 89 (8) (2007 Aug) 1010–1014, <https://doi.org/10.1302/0301-620X.89B8.19424>.
- [6] R.M. Smith, M.K. Schaefer, M.A. Kainer, M. Wise, J. Finks, J. Duwve, et al., Fungal infections associated with contaminated methylprednisolone injections, *N. Engl. J. Med.* 369 (17) (2013) 1598–1609, <https://doi.org/10.1056/NEJMoa1213978>.
- [7] P.R. Kumashi, A. Safdar, G. Chamilos, R.F. Chemaly, I.I. Raad, D.P. Kontoyiannis, Fungal osteoarticular infections in patients treated at a comprehensive cancer Centre: a 10-year retrospective review, *Clin. Microbiol. Infect.* 12 (621–6) (2006) 598–609, <https://doi.org/10.1111/j.1469-0691.2006.01471.x>.
- [8] P.G. Pappas, C.A. Kauffman, D.R. Andes, C.J. Clancy, K.A. Marr, Luis Ostrosky-Zeichner, et al., Clinical practice guideline for the management of Candidiasis: 2016 update by the Infectious Diseases Society of America, *Clinical Infectious Disease* 62 (4) (2016 Feb 15) e1–e50, <https://doi.org/10.1093/cid/civ933>.
- [9] Michael W. Henry, Andy O. Miller, Thomas J. Walsh, Barry D. Brause, Fungal musculoskeletal infections, *Infect. Dis. Clin. N. Am.* 31 (2017) 353–368, <https://doi.org/10.1016/j.idc.2017.01.006>.
- [10] H. Wisplinghoff, T. Bischoff, S.M. Tallent, H. Seifert, R.P. Wenzel, M.B. Edmond, Nosocomial bloodstream infections in US hospitals: analysis of 24,179 cases from a prospective nationwide surveillance study, *Clin. Infect. Dis.* 39 (2004) 309–317, <https://doi.org/10.1086/421946>.
- [11] C.C. Kibbler, S. Seaton, R.A. Barnes, W.R. Gransden, R.E. Holliman, E.M. Johnson, J.D. Perry, D.J. Sullivan, J.A. Wilson, Management and outcome of bloodstream infections due to Candida species in England and Wales, *J. Hosp. Infect.* 54 (2003) 18–24, [https://doi.org/10.1016/S0195-6701\(03\)00085-9](https://doi.org/10.1016/S0195-6701(03)00085-9).
- [12] D.M. Kuhn, J. Chandra, P.K. Mukherjee, M.A. Ghannoum, Comparison of biofilms formed by Candida albicans and Candida parapsilosis on bioprosthetic surfaces, *Infect. Immun. Am. Soc. Microbiol.* 70 (2002) 878–888, <https://doi.org/10.1128/IAI.70.2.878-888.2002>.
- [13] M.N. Gamaletsou, D.P. Kontoyiannis, N.V. Sipsas, B. Moritama, E. Alexander, E. Roilides, et al., Candida osteomyelitis: analysis of 207 pediatric and adult cases (1970–2011), *Clin. Infect. Dis.* 55 (2012) 1338–1351, <https://doi.org/10.1093/cid/cis660>.
- [14] F. Arias, S. Meta-Essayag, M.E. Landaeta, C.H. Capriles, C. Perez, M.J. Nunez, Candida albicans osteomyelitis: case report and literature review, *Int. J. Infect. Dis.* 8 (2004) 307–314, <https://doi.org/10.1016/j.ijid.2003.12.006>.
- [15] M.N. Gamaletsou, B. Rammaert, M.A. Bueno, N.V. Sipsas, B. Moriyama, D. P. Kontoyiannis, et al., Candida arthritis: analysis of 112 pediatric and adult cases, *Open Forum Infect Diseases* 3 (1) (2015 Dec 23), ofv207, <https://doi.org/10.1093/ofid/ofv207>.
- [16] D. Neofytos, S. Huprikar, A. Reboli, M. Schuster, N. Azie, B. Franks, et al., Treatment and outcomes of Candida osteomyelitis: review of 53 cases from the PATH Alliance(R) registry, *Eur. J. Clin. Microbiol. Infect. Dis.* 33 (2014) 135–141, <https://doi.org/10.1007/s10096-013-1939-0>.
- [17] J.E. Bennett, Echinocandins for candidemia in adults without neutropenia, *N. Engl. J. Med.* 355 (2006) 1154–1159, <https://doi.org/10.1056/NEJMct060052>.
- [18] A.R. Tunkel, C.Y. Thomas, B. Wispelwey, Candida prosthetic arthritis: report of a case treated with fluconazole and review of the literature, *Am. J. Med.* 94 (1) (1993 Jan) 100–103, [https://doi.org/10.1016/0002-9343\(93\)90127-b](https://doi.org/10.1016/0002-9343(93)90127-b).
- [19] J.H. Rex, T.J. Walsh, J.D. Sobel, S.G. Filler, P.G. Pappas, W.E. Dismukes, et al., Practice guidelines for the treatment of Candidiasis, *Clinical Infectious Diseases* 30 (4) (Apr., 2000) 662–678, <https://doi.org/10.1086/313749>.