Periprosthetic Knee Infection Caused by Candida glabrata:

A case report and literature review

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Infection following total knee arthroplasty (TKA) is a serious complication that can cause devastating consequences. The treatment of this condition involves economic and social burden[1-2]. A wide variety of pathogens are known to cause periprosthetic knee infection. The majority of infections are caused by gram-positive bacteria, of which, Staphylococcus aureus and Staphylococcus epidermidis infections occur most often[3-4]. Fungal periprosthetic knee infection is uncommon. This condition represents a therapeutic challenge because clear treatment guidelines have not yet been established. We presented a case of Candida glabrata infection following TKA which successfully managed with two-stage exchange arthroplasty.

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Case report

An 87-year-old Thai woman who had a past medical history of hypertension and dyslipidemia. She underwent left TKA due to late stage knee osteoarthritis as shown in Fig. 1. The surgery was successful with no perioperative complication. The postoperative radiographs were shown in Fig. 2.

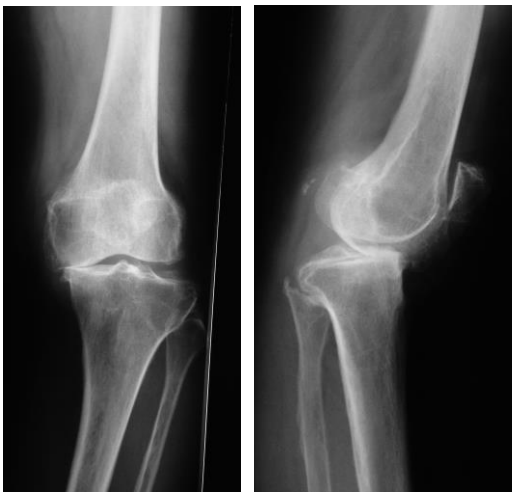

Fig. 1 Preoperative radiographs of the left knee demonstrated late stage osteoarthritic change of the left knee

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Fig. 2 Postoperative radiographs of left TKA

At 2-week follow-up (FU), the surgical wound healed nicely with no history of wound drainage. She had a straight forward early recovery in terms of full weight bearing and the arc of knee motion, including knee flexion to 110 degrees, and knee extension to 5 degrees. At 12-week FU, she reported progressive pain on the operated knee for 2 weeks. Mostly, the pain was aggravated by walking; however, she also experienced pain at rest or at night. She denied any fever or chill. The physical examination at this juncture found that her left knee was minimal swollen and warm. The knee looked erythema with obvious discoloration on the lateral side (Fig. 3). The active range of motion

decreased to 5-90 degrees. Radiographic study revealed osteolytic lesion at the medial tibial plateau under tibial base plate (Fig. 4).

Fig. 3 Abnormal local signs at the left knee at 12-week FU, including swelling, warmth and redness of skin.

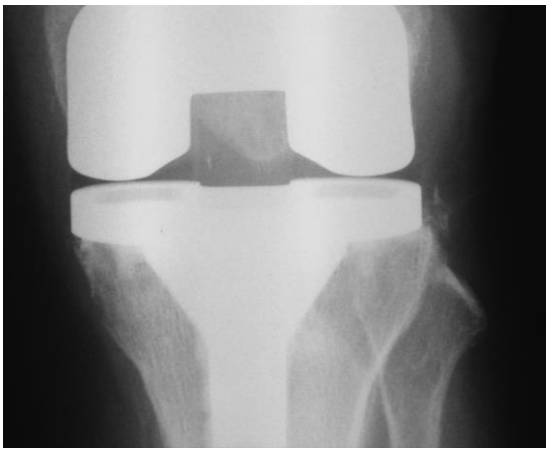

Fig. 4 Osteolytic lesion with cortical breakage at the medial tibial plateau was detected, radiographically.

Laboratory tests revealed a leukocyte blood count of 5,600 cells/μL, an erythrocyte sedimentation rate (ESR) of 69 mm/h and a C-reactive protein (CRP) of 9.5 mg/L. Aspiration of the left knee joint revealed slightly yellowish turbid fluid. The Gram stain and culture for bacteria were investigated with negative findings. However, an uncommon organism; *Candida glabrata*, was reported as the positive organism. Sensitivity test revealed this organism sensitive to amphotericin B and fluconazole.

The patient eventually underwent two-stage exchange arthroplasty. Ten days after aspiration, we underwent the 1st stage surgery. All prosthetic components were removed, thorough meticulous debridement, and antibiotic-impregnated cement spacer was implanted (Fig. 5). Two packs (80 grams) of bone cement added with 4 grams of vancomycin was used for the static spacer. Cylindrical cast was applied and partial weight bearing ambulation with walker was allowed.

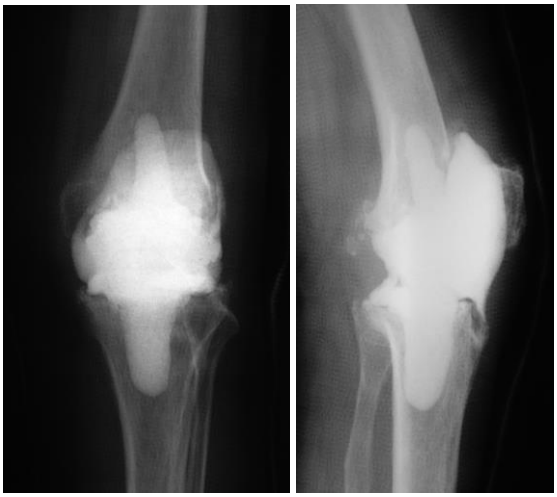

Fig. 5 Radiographs demonstrating static antibiotic-impregnated cement spacer

Intraoperative fluid and tissue cultures during the 1st stage surgery were positive for *Candida glabrata* in all 5 specimens. Histopathological examination revealed acute inflammation with lymphocytic predominate which was corresponding to acute non-bacterial infection. Amphotericin B (0.8 mg/kg/day) was administered intravenously for 6 weeks, and then 400 mg/day of fluconazole prescribed orally for additional 8 weeks. At 14 weeks after the first-stage surgery, her clinical symptom was improved with no knee pain and swelling. Laboratory tests revealed an ESR of 12 mm/h and a CRP of 0.8 mg/L. The patient then underwent the 2nd stage operation (Fig. 6).

After prosthesis reimplantation, the patient continued to receive oral fluconazole for 10 weeks. Cultures of intraoperative fluid and tissue during the 2nd stage surgery were negative in all 5 specimens. At 5 years after two-stage exchange arthroplasty, no clinical signs or laboratory tests of persistent or recurrent infection could be observed. Radiographic study showed well position of the prosthesis with no evidence of implant loosening (Fig. 7).

Fig. 6 Knee radiographs after reimplantation with varus-valgus constrained total knee system with constrained tibial polyethylene insert.

Fig. 7 Radiographs of the left knee at 5 years after reimplantation

Discussion and literature review

According to the literature, most of periprosthetic knee infections are caused by gram positive bacteria. However, recent data have showed that fungal periprosthetic joint infection could present and it has become an increasing problem in the future[5]. Patients with an immunocompromised status; such as diabetes mellitus, malnutrition, rheumatoid arthritis, and acquired immunodeficiency syndrome, etc., inappropriate or prolonged use of antibiotics, or intravenous drug abuse are thought to be predisposing to fungal infection[5]. However, Phelan et al[6] reported 40% of patients with fungal periprosthetic joint infection did not have an identifiable risk factor. Among fungal periprosthetic joint infection, the most common isolated organisms were Candida species, especially *Candida albicans* and *Candida parapsilosis* which were the commonest pathogens, whilst *Candida glabrata* was less common organism[5-7].

Candida glabrata, once known as *Torulopsis glabrata*, is a non-hyphae yeast which is considered the normal flora of the gastrointestinal tract, the genitourinary tract, and the skin of healthy individual[8]. As it is rarely the cause of serious infection in human, it has been considered a relatively nonpathogenic organism. With increasing population of immunocompromised hosts, the frequency of infection caused by this organism has been increasing significantly[9]. However, in this case report, the periprosthetic knee infection caused by this low virulent candida occurred in normal host which the authors could not identify the risk of infection.

To the best of our knowledge, there has been no standard guideline to treat fungal periprosthetic knee infection. According to the relevant literature, data demonstrated that debridement with prosthetic retention failed to control periprosthetic fungal infection in most cases[5,10,11]. However, some reports have shown successful treatment of periprosthetic fungal infection with debridement alone in the immunocompetent patients who had very early infection[12,13]. Regarding one-stage exchange arthroplasty for periprosthetic fungal infection, data were limited. Selmon GP et al[14] reported successfully treatment with this option. Recently, Ji B et al[15] reported 7 of 11 patients with chronic periprosthetic fungal infection had satisfactory outcomes with one-stage exchange arthroplasty and required no additional surgical or medical treatment for recurrence of infection. They concluded that this option could be fairly effective and achieving acceptable functional outcomes.

Successful treatment with antifungal medications alone has been reported in certain situation when the patient's condition was unsuitable to undergo surgery[16,17]. The most successful treatment which has been reported was two-stage exchange arthroplasty combined with antifungal therapy; however, the success rate was lower than that of bacterial infection. There is inconclusive data regarding the type and duration of antifungal agents used in this condition[6,18,19]. Previous reports suggested a 6-12 months duration of antifungal medication be necessary[13,20]. Recently, the Infectious Diseases Society of America[21] recommends a minimum 6-week course of an antifungal agent should be given.

In this case report, a two-stage exchange arthroplasty with implantation of an antibiotic-loaded cement spacer at the 1st stage, administration of systemic antifungal therapy for 6 weeks followed by 8 weeks of oral antifungal medication was successful for 5 years. As there has been no reliable local therapy of antifungal agents, as well as poor elution characteristics of amphotericin B and fluconazole-loaded bone cement[22-24], we decided to impregnate the bone cement with antibiotic to decrease the risk of bacterial superinfection[5,25]. According to the rule of thumb, the 2nd stage reimplantation was performed at 14 weeks after the 1st stage operation when the clinical symptoms and signs, as well as laboratory parameters, were normal. We chose amphotericin B rather than fluconazole, as a systemic antibiotic at the early phase of treatment, as some reports demonstrated that *Candida glabrata* had intrinsic resistance to fluconazole and other azole antifungal medications[9,14]. As potential side effects of amphotericin B including acute renal failure, anemia, hypokalemia, hyperpyrexia, malaise, hypotension, and occasional leukopenia and thrombocytopenia were high[9], we closely monitored this patient for the whole duration of treatment. Following a full course of systemic amphotericin B, oral fluconazole was administered according to antifungal susceptibility test, and the response for treatment was quite well.

In summary, with the sparsity of reported cases of fungal periprosthetic joint infection, there are still few data regarding the efficacy of different treatment strategies. This case report had a satisfied outcomes according to the principle of recommended treatment of fungal periprosthetic joint infection including two-stage exchange arthroplasty combined with antifungal therapy. However, the inconclusive data that need further study remains the type and duration of antifungal medication, the efficacy of local antifungal therapy, the optimal time to performed reimplantation and the long-term results of each treatment protocols.

References

1. Hanssen AD. Managing the infected knee: As good as it get. J Arthroplasty 2002; 17: 98-101.
2. Kilgus DJ, Howe DJ, Strang A. Results of periprosthetic hip and knee infections caused by resistant bacteria. Clin Orthop Relat Res 2002; 404: 116-24.
3. Lentino JR. Prosthetic joint infections: bane of orthopedists, challenge for infectious disease specialists. Clin Infect Dis 2003; 36: 1157-61.
4. Hanssen AD, Rand JA. Evaluation and treatment of infection at the site of a total hip or knee arthroplasty. Instr Course Lect 1999; 48: 111-22.
5. Azzam K, Parvizi J, Jungkind D, Hanssen A, Fehring T, Springer B, et al. Microbiological, clinical, and surgical features of fungal periprosthetic joint infections: a multi-institutionl experience. J Bone Joint Surg Am 2009; 91: 142-9.
6. Hwang BH, Yoon JY, Nam CH, Jung KA, Lee SC, Han CD, et al. Fungal periproshetic joint infection after primary total knee replacement. J Bone Joint Surg Br 2012; 94: 656-9.
7. Cardinal E, Braunstein EM, Capello WN, Heck DA. Candida albicans infection of prosthetic joints. Orthopedics 1996; 19: 247-51.
8. Phelan DM, Osmon DR, Keating MR, Hanssen AD. Delayed reimplantation arthroplasty for candida prosthetic joint infection: a report of 4 cases and review of the literature. Clin Infect Dis 2002: 34: 930-8.
9. Fidel PL Jr, Vazquez JA, Sobel JD. Candida glabrata: Review of epidemiology, pathogenesis, and clinical disease with comparison to C. albicans. Clin Microbiol Rev 1999; 12: 80-96.
10. Crockarell JR, Hanssen AD, Osmon DR, Morrey BF. Treatment of infection with debridement and retention of the components following hip arthroplasty. J Bone Joint Surg Am 1998; 80: 1306-13.
11. Silva M, Tharani R, Schmalzried TP. Results of direct exchange or debridement of the infected total knee arthroplasty. Clin Orthop Relat Res 2002; (404): 125-31.
12. Brooks DH, Pupparo F. Successful salvage of a primary total knee arthroplasty infectd with Candida parapsilosis. J Arthroplasty 1998; 13: 707-12.
13. Fukasawa N, Shirakura K. Candida arthritis after total knee arthroplasty-a case of successful treatment without prosthesis removal. Acta Orthop Scand 1997; 68: 306-7.
14. Selmon GP, Slater RN, Shepperd JA, Wright EP. Successful 1-stage exchange total knee arthroplasty for fungal infection. J Arthroplasty 1998; 13: 114-5.
15. Ji B, Zhang X, Xu B, Guo W, Mu W, Cao L. Single-stage revision for chronic fungal periprosthetic joint infection: an average of 5 years of follow-up. J Arthroplasty 2017.
16. Cushing RD, Fulgenzi WR. Synovial fluid levels of fluconazole in a patient with Candida parapsilosis prosthetic joint infection who had an excellent clinical response. J Arthroplasty 1997; 12: 950.
17. Merrer J, Dupont B, Nieszkowska A, De Jonghe B, Outin H. Candida albicans prosthetic arthritis treated with fluconazole alone. J Infect 2001; 42: 208-9.
18. Yang SH, Pao JL, Hang YS. Staged reimplantation of total knee arthroplasty after Candida infection. J Arthroplasty 2001; 16: 529-32.

19. Anagnostakos K, Kelm J, Schmitt E, Jung J. Fungal periprosthetic hip and knee joint infections clinical experience with a 2-stage treatment protocol. J Arthroplasty 2012; 27: 293-8.
20. Tunkel AR, Thomas CY, Wispelwey B. Candida prosthetic arthritis: report of a case treated with fluconazole and review of the literature. Am J Med 1993; 94: 100-3.
21. Pappas PG, Kauffman CA, Andes D, Benjamin DK Jr, Calandra TF, Edwards JE Jr, et al. Clinical practice guidelines for the management of candidiasis: 2009 update by the Infectious Diseases Society of America. Clin Infect Dis 2009; 48: 503-35.
22. Goss B, Lutton C, Weinrauch P, Jabur M, Gillett G, Crawford R. Elution and mechanical properties of antifungal bone cement. J Arthroplasty 2007; 22: 902-8.
23. Marra F, Robbins GM, Masri BA, Duncan C, Wasan KM, Kwong EH, et al. Amphotericin B-loaded bone cement to treat osteomyelitis caused by Candida albicans. Can J Surg 2001; 44: 383-6.
24. Kuhn DM, Chandra J, Mukherjee PK Ghannoum MA. Comparison of biofilms formed by Candida albicans and Candida parapsilosis on bioprosthetic surfaces. Infect Immun 2002; 70: 878-8.
25. Silverberg D, Kodali P, Dipersio J, Acus R, Askew M. In vitro analysis of antifungal impregnated polymethylmethacrylate bone cement. Clin Orthop Relat Res 2002; (403): 228-31.

ภาวะติดเชื้อหลังการผ่าตัดเปลี่ยนข้อเข่าเทียมจากเชื้อ Candida Glabrata: รายงานผู้ป่วยและการทบทวนผลงานวิจัย

มนูญ ศักดินาเกียรติคุณ, พบ, อารี ตนาวลี, พบ

ภาวะติดเชื้อหลังการผ่าตัดเปลี่ยนข้อเข่าเทียมเป็นภาวะแทรกซ้อนร้ายแรงที่อาจส่งผลเสียตามมา การติดเชื้อส่วนใหญ่เกิดจากเชื้อแบคทีเรียแกรมบวก โดยเชื้อที่พบบ่อยที่สุดได้แก่เชื้อ Staphylococcus aureus และเชื้อ Staphylococcus epidermidis การติดเชื้อหลังการผ่าตัดเปลี่ยนข้อเข่าเทียมจากเชื้อราพบได้ไม่บ่อย แต่เป็นภาวะที่ยากต่อการรักษา เนื่องจากยังไม่มีแนวทางมาตรฐานในการรักษาภาวะดังกล่าว ผู้ทำงานวิจัยและคณะได้นำเสนอรายงานผู้ป่วยที่ติดเชื้อหลังการผ่าตัดเปลี่ยนข้อเข่าเทียมจากเชื้อ Candida Glabrata และได้รับการรักษาโดยวิธี two-stage exchange arthroplasty

ผู้ป่วยหญิงไทย อายุ 87 ปี ได้รับการผ่าตัดเปลี่ยนข้อเข่าเทียมข้างซ้ายจากภาวะข้อเข่าเสื่อมระยะท้าย หลังการผ่าตัดผู้ป่วยสามารถเดินลงน้ำหนักได้ดี เมื่อครบสองสัปดาห์หลังการผ่าตัดผู้ป่วยสามารถงอเข่าข้างผ่าตัดได้หนึ่งร้อยสิบองศา แผลผ่าตัดหายปกติดี แต่เมื่อถึงระยะเวลาสามเดือนหลังการผ่าตัด ผู้ป่วยมีอาการปวดเข่าข้างที่ทำผ่าตัด เข่าบวมแดงและอุ่น ผู้ป่วยงอเข่าได้ลดลงเหลือเก้าสิบองศา ภาพถ่ายทางรังสีพบว่ามี osteolytic lesion with cortical breakage ที่ตำแหน่ง medial tibial plateau ผลการตรวจเลือดทางห้องปฏิบัติการพบว่าค่า erythrocyte sedimentation rate (ESR) เท่ากับ 69 มิลลิเมตรต่อชั่วโมง และค่า C-reactive protein (CRP) เท่ากับ 9.5 มิลลิกรัมต่อลิตร ผลการเจาะเข่าพบน้ำภายในข้อเข่าสีเหลือง ขุ่นเล็กน้อย นำไปส่งตรวจเพาะเชื้อ พบเชื้อ Candida Glabrata คณะผู้ทำงานวิจัยได้ให้การรักษาโดยวิธี two-stage exchange arthroplasty ในระยะที่หนึ่งได้ผ่าตัดเอาข้อเข่าเทียมออกทั้งหมด นำน้ำและเนื้อเยื่อในข้อเข่าส่งตรวจเพาะเชื้อ ล้างทำความสะอาดภายในข้อเข่า และใส่ซีเมนต์ผสมยาปฏิชีวนะไว้ในข้อเข่า หลังผ่าตัดได้ใส่เฝือกให้กับผู้ป่วยและให้ผู้ป่วยเดินลงน้ำหนักได้บางส่วน ผลการตรวจเพาะเชื้อจากน้ำและเนื้อเยื่อภายในข้อเข่า พบเชื้อ Candida Glabrata ซึ่งไวต่อยา Amphotericin B และ fluconazole ทางคณะผู้ทำงานวิจัยจึงได้ให้ยา Amphotericin B ทางหลอดเลือดดำเป็นเวลาหกสัปดาห์ และให้รับประทานยา fluconazole ต่ออีกแปดสัปดาห์ เมื่อครบสิบสี่สัปดาห์หลังจากการผ่าตัดระยะที่หนึ่ง ผู้ป่วยไม่มีอาการปวด แผลผ่าตัดหายปกติ เข่าไม่บวมแดง ผลการตรวจเลือดทางห้องปฏิบัติการพบว่าค่า erythrocyte sedimentation rate (ESR) เท่ากับ 12 มิลลิเมตรต่อชั่วโมง และค่า C-reactive protein (CRP) เท่ากับ 0.8 มิลลิกรัมต่อลิตร ทางคณะผู้ทำงานวิจัยจึงได้ทำผ่าตัดระยะที่สอง โดยเอาซีเมนต์ผสมยาปฏิชีวนะออก ล้างทำความสะอาดภายในข้อเข่า นำเนื้อเยื่อในข้อเข่าส่งตรวจเพาะเชื้อ และใส่ข้อเข่าเทียมชนิด constrained condylar TKA ผลการตรวจเพาะเชื้อเนื้อเยื่อไม่พบเชื้อ หลังการผ่าตัดให้ผู้ป่วยรับประทานยา fluconazole เป็นเวลาสิบสัปดาห์ หลังการผ่าตัดผู้ป่วยอาการปกติดี ที่ระยะเวลาห้าปีหลังการผ่าตัดผู้ป่วยไม่มีอาการปวด ตรวจเข่าไม่พบความผิดปกติ ตรวจภาพถ่ายทางรังสีไม่พบการเปลี่ยนตำแหน่งหรือการหลุดหลวมของข้อเทียม