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ORIGINAL PAPER

Candida glabrata-Induced Refractory Infectious Arthritis: A Case Report and Literature Review

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Abstract The incidence of deep fungal infection due to *non-albicans Candida* species (especially *Candida glabrata*) has significantly increased in recent decades. *Candida glabrata* is an opportunistic pathogen of low virulence which mainly invades the gastrointestinal, genitourinary, and respiratory tracts, but has rarely been reported as complication of articular surgery in the literature. We present a case of knee fungal arthritis caused by *C. glabrata* after a minimally invasive arthroscopic surgery. In this case, the patient's knee got infected after arthroscopic treatment for a recurrent popliteal cyst, and she was unable to be cured by either debridement or antifungal drugs. Mycological and molecular identification of the necrotic tissues isolate revealed *C. glabrata* as etiologic agent. We originally planned to conduct a debridement once again, but it was found that the articular cartilage was extensively damaged during the operation. Besides, the magnetic resonance imaging of the affected knee also showed that the infection had invaded the subchondral bone. So we treated this case with a two-stage primary total knee arthroplasty with an antibiotic-laden cement spacer block. After a 10-month follow-up, the patient had completely recovered and has not experienced any recurrence to date. In addition, we review 21 cases of *C. glabrata*-induced infectious arthritis described to date in the literature.

Keywords *Candida glabrata* · Arthritis · Fungal infection · Spacer · Antifungal resistance

Introduction

Candida glabrata mainly causes systemic or mucosal infections in immunosuppressed patients due to the increased use of prophylactic antifungal treatment [1]. Infectious arthritis induced by *C. glabrata* after arthroscopic surgery has rarely been reported before [2, 3]. Here we would like to share a refractory *C. glabrata*-induced infectious knee case with extensive cartilage damage following an arthroscopic surgery for treating a recurrent popliteal cyst. According to our experience, our measure can be borrowed for complicated, refractory mycotic arthritis which failed by debridement or systemic antifungal treatment. And at the ending of this paper, a literature review of similar cases was analyzed.

Shu Chen, Yi Chen and Yi-qin Zhou have contributed equally to this work.

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Case Report

A 58-year-old woman was admitted for chronic pain, exudation, and poor wound healing of her left knee for 6 months after arthroscopy which was performed to deal with a recurrence of popliteal cyst (21 * 10 * 9 mm^3) at the local hospital. However, redness, swelling, and effusion were observed around the affected knee from 15 days after the operation. All of the treatments including superficial debridement, irrigation, and a 2-month course of oral fluconazole did not work. The wound gradually formed an irregularly shaped abscess and a sinus tract with effusion. Her past medical history included diabetes mellitus with poor blood glucose control and chronic hepatitis B.

Physical examination revealed the presence of an 4.5 cm × 5.0 cm irregularly shaped abscess on the medial side and a circular sinus tract in diameter of 2 cm on the lateral side of her left knee (Fig. 1). Radiographs (X-ray and MRI) of the knee showed extensive destruction of the subchondral bone, popliteal cyst, and joint cavity effusion (Fig. 2). An articular cavity puncture was conducted firstly, and the puncture fluid and wound secretion were cultured. In the meantime, intravenous fluconazole (0.2 g/day) was empirically used initially. The inflammation marker showed C-reactive protein 40 mg/l and erythrocyte sedimentation rate 48 mm/h, and the G test result was 158 pg/ml.

A thorough debridement was originally planned to conduct once again. However, it was found that the knee articular cartilage was extensively damaged intraoperatively. So a two-stage surgical method was conducted to treat this case which is similar to our previous method to treat severe infectious arthritis caused by bacteria [4]. At the first stage, we conducted the osteotomy of distal femur and proximal tibia, then placing a well-designed antibiotic-laden bone cement spacer, combining it with a systematic antifungal drugs application to completely wipe out the pathogen.

The static cement antibiotic-loaded spacer was implanted with a total of 9 g of vancomycin, 2 g of gentamicin, and 200 g of cement. Postoperative radiographs showed a well-fixed static spacer (Fig. 3). Joint immobility of 6 weeks was executed. The histopathology stained with H&E showed hyperplastic and degenerative synovial tissue with extensive necrosis and peripheral granulomatous changes (Fig. 4). On Sabouraud dextrose agar (SDA), the isolate formed shining, smooth, and cream-colored colonies. Acid-fast staining and bacterial cultures were negative. The isolate was sensitive to fluconazole (minimum inhibitory concentration [MIC], 1 μg/ml), itraconazole (MIC, 0.125 μg/ml), voriconazole (MIC, 0.06 μg/ml), and amphotericin B (MIC, 0.5 μg/ml). For species molecular sequencing, the internal transcribed spacer (ITS) rRNA gene was analyzed by PCR using primers ITS1 and ITS4. Amplification was carried out at 94 °C for 5 min, followed by 30 cycles of 94 °C for 30 s, 55 °C for 30 s, and 72 °C for 1 min,

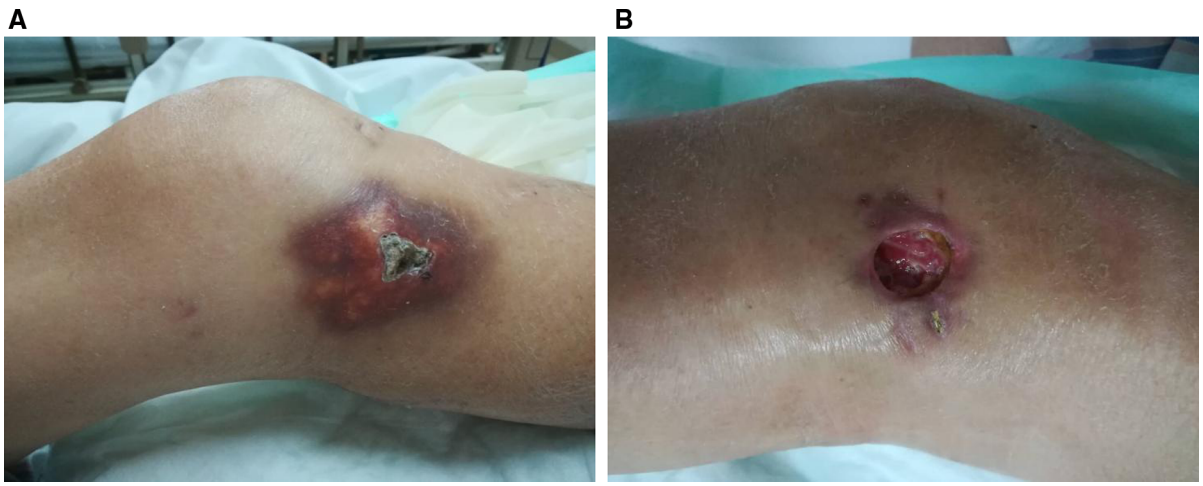

Fig. 1 Appearance of the left knee at admission. **a** An irregularly shaped abscess on the medial side. **b** A circular sinus tract in diameter of 2 cm on the lateral side

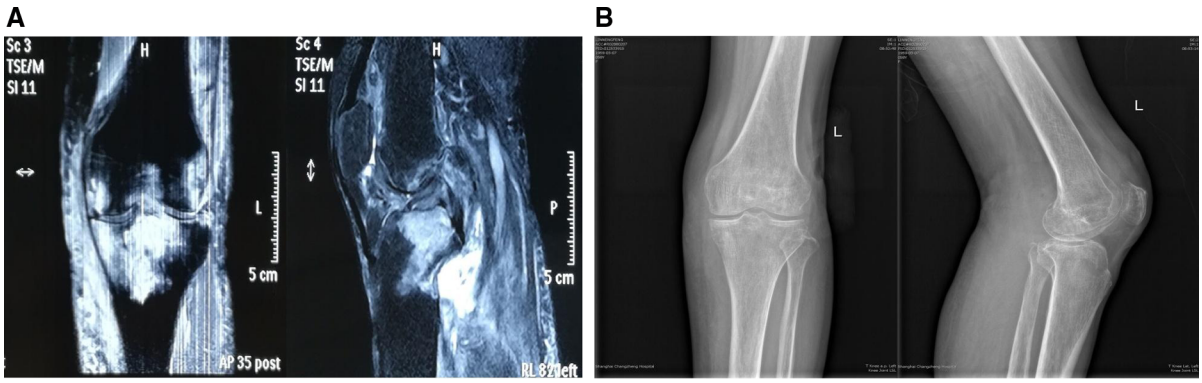

Fig. 2 Radiographs of the knee revealing extensive destruction and bone marrow edema of the femur and tibia, osteoarthritis, popliteal cyst, joint cavity effusion. **a** Sagittal and coronal images of MRI. **b** X-rays of the knee

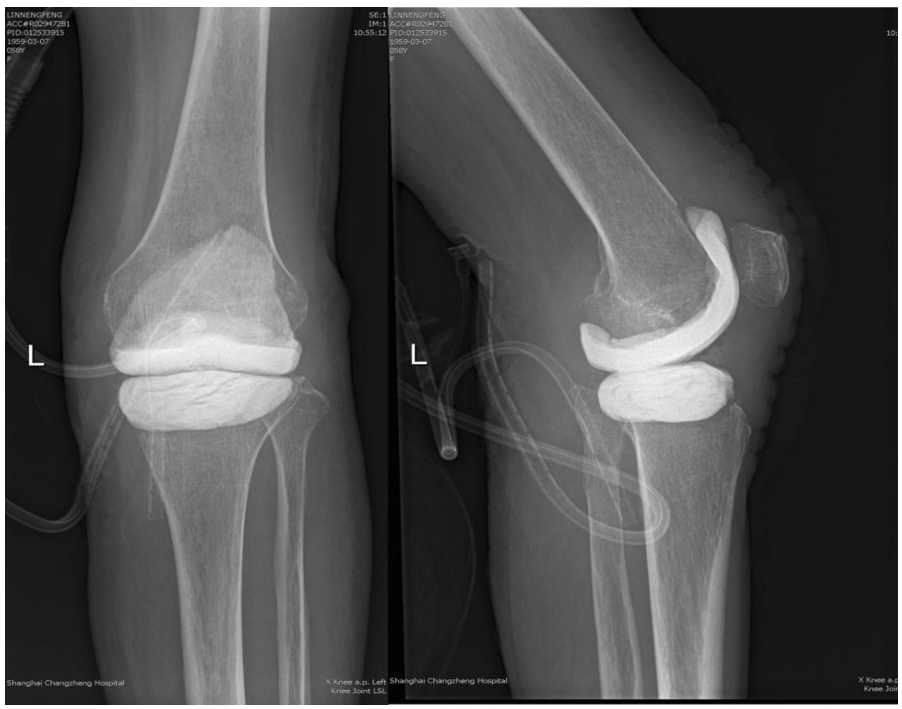

Fig. 3 Postoperative radiographs showing well-fixed static spacer

with a final extension at 72 °C for 7 min 30 s. The PCR products were sequenced by the Shanghai Majorbio Company. The results showed that the fragment was consistent with a fragment from *C. glabrata* by submitting the gene sequence to BLAST for nucleotide comparison (homology was 100%; Genebank Number SCZ91521) tool (BLAST) algorithm (https://blast.ncbi.nlm.nih.gov/Blast.cgi) of the National Centre for Biotechnology Information (NCBI).

Amphotericin B was suggested to be the optimal treatment for this condition after consultation with infectious disease specialists and dermatologists. The creatinine was rapidly rose to 232 μmol/l after intravenous infusion of amphotericin B for 2 weeks (lipid formulation, 0.4 g/day). So intravenous application of voriconazole (0.16 g/day) had been treated instead for 3 months, and inflammatory markers (ESR and CRP) were monitored (Fig. 5). After the infection was eradicated (all inflammatory markers were negative,

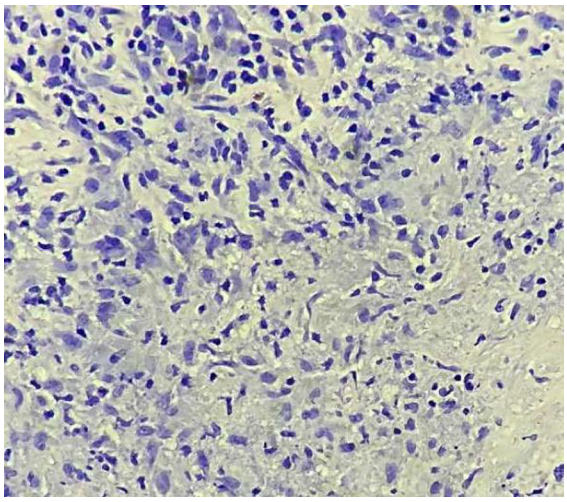

Fig. 4 Histopathology stained with H&E showed hyperplastic and degenerative synovial tissue with extensive necrosis and peripheral granulomatous changes

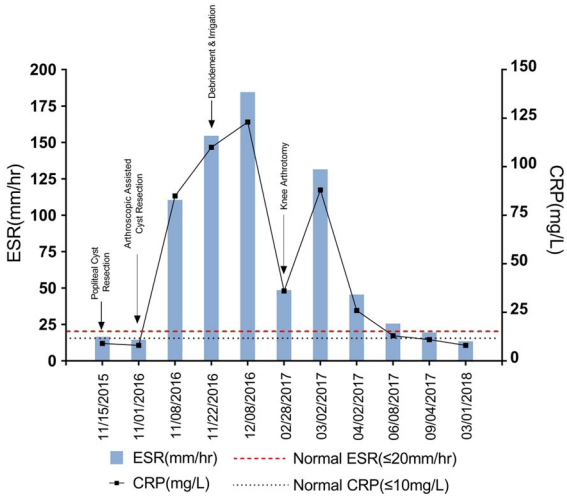

Fig. 5 Inflammatory markers (ESR and CRP) were monitored

and no inflammatory symptom was observed), the second stage of a primary total knee arthroplasty was conducted 1 year after the arthrotomy to reestablish the knee function (Fig. 6). At a follow-up of 10 months, no persistence of infection or reinfection is observed.

Discussion

Arthroscopic knee surgery is minimally invasive and safe with low complication incidences (0.27–4.7% [5–7]). Infections of any kind are rarely reported yet the nerve-wracking complication of this surgery (0.84% [5]), especially with the fungal infection did occur. Overall incidence of fungal arthritis is relatively low due to *non-albicans Candida* species which is less than 1% of all arthritis cases but has increased in recent years due to the increasing application of corticosteroid, overuse of antibiotics, aging, and diabetes [8], although *Candida albicans* is still the most widespread isolated species and is the main pathogen of fungal knee arthritis [9]. *Candida glabrata* is a kind of special fungal species due to its acquisitive antifungal resistance, which may cause a devastating complication of articular surgery (such as arthroplasty, arthroscopy, and internal fixation). The progress of the *C. glabrata* infection is too hard to manage that leads to substantial utilization of healthcare resources. *Candida glabrata* is of special significance due to its upward trend in acquisitive antifungal resistance among *Candida* species [1].

Candida glabrata displays several virulence factors (adherence, biofilm formation, and secretion of hydrolytic enzymes), swelling their persistence within the host, triggering host cell damage, and finally, resulting in clinical and microbiological failure. Therefore, the increase in the incidence and antifungal resistance of *C. glabrata* leads to high morbidity and mortality. It has low sensitivity to common antifungal drugs and can rapidly develop resistance to fluconazole. The resistance rate is on the rise. These mechanisms cover all antifungal classes, but mostly the azoles, which are the most commonly used by physicians, in both ambulatory and hospital environments. As long as the various classes of antifungals are being used therapeutically or prophylactically, and sometimes indiscriminately, resistance mechanisms are emerging and the therapeutic solutions becoming narrower. *Candida glabrata* only grows in the yeast form. So it is lacking a yeast-to-hyphae switch, which is one of the main virulence factors of *C. albicans*.

A total of 21 *C. glabrata* arthritis cases have been found available in the PubMed database retrieved by the keyword of "*Candida glabrata*" and "fungal infection" or "arthritis" [2, 10–27]. The mean age at diagnosis was 61 (± SD 14) years, 16 of which (76.19%) are over 50 years. Thirteen cases occurred in the hip, 7 in the knee, 1 in the shoulder, and 1 in the ankle (accompanied by infection of the knee). Fourteen cases had risk factors for fungal septic arthritis,

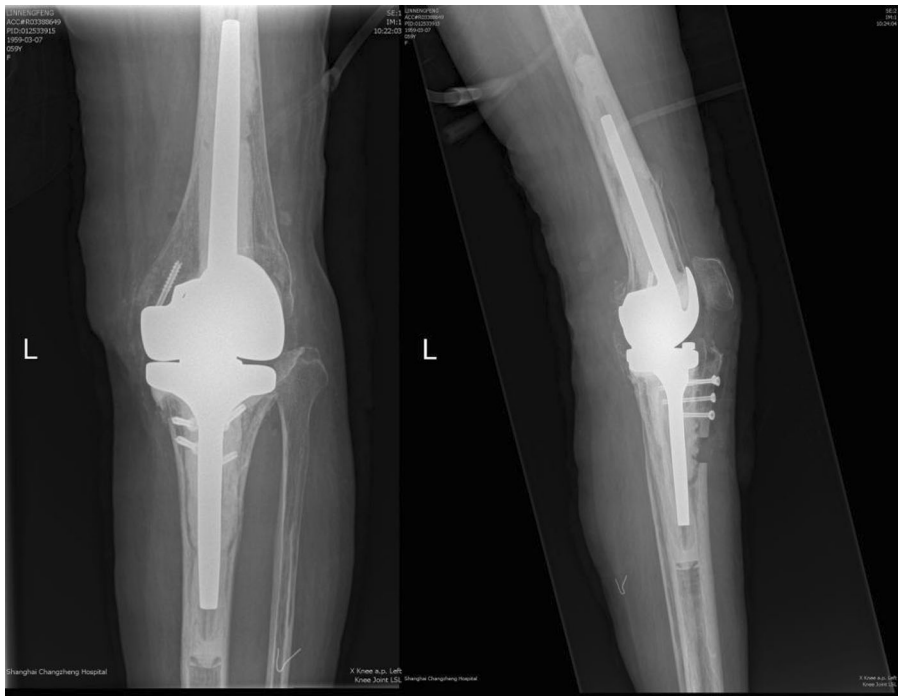

Fig. 6 Postoperative radiographs showing well-fixed prosthesis

and the main risk factors include systemic disease (e.g., rheumatoid arthritis, systemic lupus erythematosus) and/or immunosuppressive therapy in 7 (33.3%) cases, diabetes mellitus in 3 (14.3%), long-term antibiotic use in 3 (14.3%), chronic steroids in 4 (19.1%) cases, and arthroplasty in 18 (85.7%) cases. There were 18 periprosthetic joint infections (12 hip arthroplasties, 5 knee arthroplasties, 1 humeral hemiarthroplasty). Only 3 cases were infected without any implant (1 case was after the meniscectomy, 1 was after the orthotopic liver transplantation, and 1 was primary knee joint infection without previous surgery). Due to increased predisposing factors, the risk of such infections has increased as well [9]. The main clinical manifestations were pain, swelling, fever, and exudation.

The diagnosis of fungal arthritis can often be delayed or neglected due to lack of awareness or negative growth [28]. The value of inflammatory tests such as ESR and CRP in the diagnosis is limited. DNA tests are highly specific and can assist in the identification of the fungus in more expedite ways. The diagnosis can also be made by serology, biopsy, an enzyme immunoassay test and intradermal reaction to histoplasmin. It is not possible to confirm whether the arthritis was indeed caused by contaminated skin or instruments in the arthroscopic procedure. It might as well have been the result of temporary immune compromise caused by the surgical procedure in an already infected but asymptomatic individual. It is also hard to judge whether infection was formed after the first cystectomy although there is no any symptom or sign at that time in this case. The synovial fluid culture is the gold standard of diagnosis and may show positivity in up to 92% [9], but this fungus takes approximately 6 weeks to grow in vitro.

It is difficult to treat the *C. glabrata* arthritis, and it should be determined by the results of antimicrobial susceptibility testing and mainly includes antifungal drugs and surgical intervention. However, there is no consensus on whether antifungal therapy alone or combined debridement should be conducted when deep fungal infection occurs. The choice of surgical treatment depends on the extent of infection, the exist of implant and the variety of implant. Seventeen cases of infection after arthroplasty were treated by surgical or arthroscopic debridement. The prosthesis of 14 cases was removed, 2 cases were treated with one-stage revision, 10 cases were placed with bone cement spacer, and 5 cases were treated with antibiotic bone

Table 1 A brief on the clinical features of *Candida glabrata* arthritis in the literature

	Age/sex	Previous surgery	Localization of infection	Comorbidities	Surgical infection treatment	Impregnation of bone cement	Antimicrobial therapy	Complications	Follow-up (mo)
Goodman et al. [18]	69/F	THA	Hip	NRa	Removal, resection arthroplasty	NR	Amphotericin B irrigation (7d)	NR	NR
Darouiche [14]	69/F	THA	Hip	None	Removal	No	Irrigation with amphotericin B (75 mg qd, 7d)	None	NR
Nayeri et al. [22]	62/F	rTHA	Hip and kidney	Obesity, non-insulin-dependent diabetes, renal calculus, pyelonephritis and massive hemataria, previous antibiotic treatment	rTHA	No	Flucytosine (6 g qd, 12d), amphotericin B (50 mg qd, 12d), ciprofloxacin, netilmicin, and fluconazole (2 w), flucytosine (1.5 g qd, 4d) and itraconazole (2w)	Renal dysfunction	7
Selmom et al. [24]	75/F	TKA	Knee	Duodenal ulcer, emergency abdominal surgery	One-stage exchange arthroplasty	Yes	Amphotericin B (1w), oral itraconazole (200 mg bid, 8w)	None	48
Gumbo et al. [34]	34/M	Orthotopic liver transplantation	Hip	Liver cirrhosis	Surgical debridement	No	Intravenous amphotericin B (2500 mg)	None	18
Zmierczak et al. [27]	40/M	None	Ankle and knee	Cohol abuse, gout and corticoid-dependent COPD, previous antibiotic treatment	Repeated arthrocentesis and joint lavage with 0.9% saline solution	NO	Intravenous amphotericin B (50 mg, qw), oral itraconazole	Renal failure and anorexia	NR
Ramamohan et al. [23]	65/F	rTHA	Hip	None	Two-stage revision	No	Intravenous amphotericin B in escalating doses, amiloride, 5-flucytosine	None	24
Acikgoz et al. [10]	70/F	TKA	Knee	None	Removal, spacer, arthrodesis	No	Oral fluconazole (200 mg bid)	None	7
Gaston and Ogden [17]	42/F	Bilateral TKA	Knee	Lupus treated with chronic steroids, severe pneumonia and acute renal failure	Extensive irrigation and debridement with component removal and placement of an antibiotic spacer, lastly above-knee amputation	Yes	Variconazole (2 m) supplemented with intra-articular amphotericin B	None	6

Table 1 continued

	Age/sex	Previous surgery	Localization of infection	Comorbidities	Surgical infection treatment	Impregnation of bone cement	Antimicrobial therapy	Complications	Follow-up (mo)
Lejko-Zupanc et al.[21]	73/M	THA	Hip	Diabetes	Hip spacer and extensive debridement	Yes	Conventional amphotericin (2500 mg), liposomal amphotericin (11.1 g), caspofungin (50 mg qd, 3w)	Significant rise of blood urea nitrogen, persistent anemia	36
Fabry et al. [16]	74/F	TKA	Knee	Undergone coronary by pass surgery, duodenal ulceration, cholecystitis	Drained and irrigated with 9 L of physiological saline solution, second debridement	No	Voriconazole	NR	7
Dumaine et al. [15]	72	THA	Hip	Rheumatoid arthritis treated by corticoids and leflunomide	Removal, total synovectomy and resection	No	Caspofungin (70 mg then 50 mg bid, 14d), flucytosine (2.5 g bid, 14d), oral fluconazole (400 mg qd, 4 m), oral flucytosine	NR	15
Anagnostakos et al. [11]	51/F	rTHA	Hip	COPD, hepatitis B, endogenous, psychosis, cutaneous mycosis, nicotin use	Hip spacer	1 g gentamicin + 4 g vancomycin/80 g bone cement	Fluconazole (6w)	Central venous catheter infection after spacer and prosthesis reimplantation, respectively; draining sinus after prosthesis reimplantation	70
Anagnostakos et al. [11]	78/M	rTHA	Hip	Art. hyperton, heartpacemaker, myocar dial infarction, cerebralinfarction, obstructive sleep apnea, myelodysplastic syndrome	Hip spacer	1 g gentamicin + 4 g vancomycin/80 g bone cement	Fluconazole (6w)	Draining sinus after prosthesis reimplantation	15
Bartalesi et al. [12]	60/M	rTHA	Hip	None	Two-stage exchange arthroplasty	Gentamicin	Voriconazole (13w), caspofungin (70 mg loading dose, followed by a maintenance dosage of 50 mg qd), liposomal amphotericin B (3 mg/kg,), deoxycolate amphotericin B (50 mg qw)	NR	48

Table 1 continued

	Age/sex	Previous surgery	Localization of infection	Comorbidities	Surgical infection treatment	Impregnation of bone cement	Antimicrobial therapy	Complications	Follow-up (mo)
Hall et al. [19]	60/F	Internal screw fixation and THA	Hip	Rheumatoid arthritis, a cerebrovascular accident, previous deep vein thrombosis and vasculitis and small bowel ischemia with consequential fitting of an ileostomy bag	Arthroscopic washout and Girdlestone's procedure	No	Intravenous ceftazidime (2 g bid, 6w), caspofungin (50 mg qd), oral ciprofloxacin (750 mg twice a day)	None	NR
Zhu et al. [26]	44/M	Bilateral THA	Hip	NR	Debridement of soft tissues	NR	I.V. amphotericin B (side effects) Oral voriconazole (6	NR	3
Skedros et al. [25]	58/M	Humeral hemiarthroplasty	Shoulder	Insulin-dependent diabetes, hypertension, sleep apnea, COPD, and a history of two minor strokes (causing mild gait ataxia)	Shoulder spacer	Amphotericin B	Oral fluconazole	NONE	14
Erami et al. [2]	40/M	Meniscectomy	Knee	None	None	No	Intravenous amphotericin B (4w), oral itraconazole (2 m)	None	12
Cobo et al. [13]	77/F	rTHA	Hip	Rheumatoid arthritis (treatment with metothrexate and steroids), alcohol hepatopathy, previous antibiotic treatment	Debridement of soft tissues	No	Caspofungin, fluconazole	None	5
Koutserimpas et al. [20]	68/F	TKA	Knee	Splenectomized smoker, COPD, and alcoholism	Removal, spacer	Vancomycin and gentamycin	Voriconazole (6 m), moxifloxacin (3 m)	None	4

NR Not reported

cement. The main antibiotics used were gentamicin and vancomycin. Because of the poor thermal stability of antifungal agents such as amphotericin B, they were seldom added to bone cement. The cases infected without any prosthesis were mainly treated with debridement or lavage (one was treated with debridement, one was treated by repeated lavage with saline, and one was treated with drugs merely). One patient lastly underwent amputation. In this case, as *Candida* osteomyelitis and popliteal fossa abscess were formed, merely arthroscopic debridement was not enough [29]. What is more, the previous debridement, superficial irrigation, and antifungal agents all failed, the articular cartilage was extensively damaged, and thus, we use a two-stage surgical method described above to treat this case since *C. glabrata* has been reported to be more resistant to antifungal drugs (especially azoles) than other Candida spp. [30]. A medical treatment program should be determined by the results of antimicrobial susceptibility testing, and it must be made in consultation with infectious disease specialists. The guidelines developed by the Infectious Diseases Society of America recommend that *Candida* arthritis should be treated for at least 6 weeks with fluconazole at a dosage of 400 mg daily or with a lipid formulation of amphotericin B at a dosage of 3–5 mg/kg daily for at least 2 weeks, followed by fluconazole at a dosage of 400 mg daily. *Candida glabrata* has varied sensitivity patterns to the newer azoles. It is usually considered to be resistant to fluconazole but is often sensitive to itraconazole, although resistance is becoming a problem in some centers. The presence of an implant caused the production of a *Candida* biofilm, which limited the action of the antifungal drugs. It seems most proper that echinocandins should be first-line agents, due to their fungicidal activities against *Candida* species and biofilm produced by *Candida* strains, as well as their safety profile. The common drugs of choice are amphotericin B (conventional or lipid formulation) and voriconazole [31]. However, amphotericin B has many side effects and may not be useful for long-term therapy. On the other hand, voriconazole has good synovial fluid penetration and excellent bioavailability and is less nephrotoxic than amphotericin B [32]. Although recently in vitro study showed good elution of voriconazole from PMMA, compressive strength of the cement progressively decreases with elution. Since there is no general consensus regarding the type and dose of antifungal agents that can be mixed with cement, we have not used any antifungal agents in the cement spacer [33]. The ideal duration and route of administration of antimicrobial therapy have not been determined. However, most protocols have included 6 weeks of parenteral therapy.

It is obvious that there is no enough experience regarding a proper treatment, with this type of infection. Early diagnosis and choice of appropriate treatment, based on the cultures' results, along with surgical debridement are of paramount importance. The cure of the infection was achieved in all but 1 case who needed above-knee amputation, and 1 case died from other diseases. Six patients with recurrent infection after initial control were followed up for 3–48 months.

Conclusion

Any case clinically suspected to be caused by fungi should be confirmed by mycological tests. This case report shows once more that *C. glabrata*-induced infectious arthritis is still very difficult to treat and is a potentially devastating complication. It is of utmost importance to report these cases, since there is no consensus yet of the proper antifungal treatment in IFIs. We should be aware of the possibility of fungal arthritis in receiving therapy with arthroscopy. The antifungal drugs, together with surgical intervention, are the effective therapies for a fungal arthritis. The surgical treatment methods include continuous irrigation, arthroscopy flush, debridement, and removal of prosthesis. But for cases with wide damage of cartilage or formation of osteomyelitis, the therapy of osteotomy of proximal tibia and distal femur, placement of a antibiotic bone cement spacer, then a two-stage arthroplasty, combination with systematic antifungal drugs simultaneously, proved to be safe and effective in clearing the infection (Table 1).

Compliance with Ethical Standards

Conflict of interests The authors have no conflicts of interest to report.

Ethics Approval This study was proved by the Shanghai Chanzheng Hospital Ethics Committee.

Informed Consent Informed written consent was obtained from the patient prior to publication of the case details.

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