

REVIEW ARTICLE

Aspergillus fumigatus infection as a delayed manifestation of prosthetic knee arthroplasty and a review of the literature

MESUT YILMAZ¹, BILGÜL METE², REŞAT ÖZARAS², GÖKHAN KAYNAK³, FEHMI TABAK², YÜKSEL TENEKECİOĞLU³ & RECEP ÖZTÜRK²

From the ¹Department of Infectious Diseases and Clinical Microbiology, Istanbul Medipol University, ²Department of Infectious Diseases and Clinical Microbiology, Cerrahpaşa Medical Faculty, Istanbul University, and ³Department of Orthopaedics and Traumatology, Cerrahpaşa Medical Faculty, Istanbul University, Istanbul, Turkey

Abstract

Fungal infection after total joint arthroplasty is a very rare but serious complication and a challenge to the treating and consulting physicians. The literature includes little information about the treatment protocol for Aspergillus infection after total knee arthroplasty, since only 3 cases have been reported. We describe the case of a non-immunocompromised patient who lacked predisposing risk factors and presented with pain and swelling. An aspiration under sterile conditions revealed Aspergillus fumigatus. The patient was treated successfully with a 2-stage exchange reimplantation and 6-week course of liposomal amphotericin B. At 4 y after reimplantation, the patient had no evidence of infection or pain.

Keywords: *Aspergillus fumigatus*, prosthetic infection, total knee arthroplasty, amphotericin B

Introduction

Prosthetic joint replacement is and will be increasingly used to alleviate pain and increase mobility in patients with end-stage arthritis. The annual rate of total knee arthroplasty, the most cost-effective procedure for such patients, is expected to double by 2025 [1]. Prosthetic joint infections (PJIs) occur less frequently than aseptic failures but represent the most devastating complications. Although the use of perioperative antimicrobial prophylaxis and a laminar airflow surgical environment has reduced the risk of intraoperative infection to less than 2% after knee replacement, infections associated with prosthetic joints cause significant morbidity, account for a substantial proportion of healthcare expenditures and remain a therapeutic dilemma for healthcare providers in all fields [2]. Most commonly coagulase-negative staphylococci, Staphylococcus aureus, Streptococcus species and Gram-negative bacilli are identified as pathogens [3,4]. PJIs with fungal agents are scarce in the literature, representing 1% of orthopaedic metalware infections, and often occur in immunocompromised patients. Candida

species are the most commonly reported fungal infections [5–8]. We found 3 documented Aspergillus PJIs in our PubMed search (1979–2010) of the medical literature, 2 of which were due to A. fumigatus.

We present the third case of a PJI by A. fumigatus in an immunocompetent patient who lacked any predisposing risk factors. The patient was treated successfully with a 6-week course of liposomal amphotericin B and a 2-stage exchange reimplantation.

Case report

In July 2006, an 81-y-old man presented with complaints of pain and swelling of his right knee. The patient had undergone a bilateral total knee arthroplasty 1 y prior for osteoarthritis that had not responded to conservative management. According to his history, the first few months after the arthroplasties had been problem-free. Soon after that, however, he had become crippled by increasing pain and decreasing range of motion on the right side. He was referred to our tertiary care centre for evaluation and

management. A review of organ systems was normal and there was no history of fistula, erythema, fevers, pruritis, rashes, discharge, or trauma. The patient denied prolonged antibiotic use, extended hospitalization, poor nutritional status and steroid use, and had no other chronic illnesses. The patient's social history was unremarkable; no history of smoking, no alcohol or intravenous drug history was discovered. The patient, a retired farmer, lived with his family in a rural setting.

On physical examination, the patient was afebrile and had swelling of his right knee, but lacked erythema and purulent drainage. Results of laboratory tests included C-reactive protein (CRP) of 40 mg/l (normal range 0–5), a white blood cell (WBC) count of $7.1 \times 10^9/l$, neutrophils 60%, haematocrit 0.30, blood urea nitrogen (BUN) 29 mg/dl, creatinine 1.1 mg/dl, and an erythrocyte sedimentation rate (ESR) of 108 mm/h.

During his workup, the right knee was aspirated under sterile conditions. Gram stain and cultures were negative for aerobic pathogens, but surprisingly positive for filamentous fungi. With the suspicion that the isolated mould could be a contaminant, a repeat knee aspiration performed 10 days after the initial one confirmed heavy growth of *A. fumigatus*. *Aspergillus* species were identified with colony morphology and microscopic appearance, and tested for susceptibility to amphotericin B by the Clinical and Laboratory Standards Institute (CLSI) reference broth microdilution method [9]. *A. fumigatus* was susceptible to amphotericin B with a minimum inhibitory concentration (MIC) of 0.25 µg/ml.

Nuclear imaging studies were performed in order to confirm PJI in July 2006, and showed increased periprosthetic uptake and increased periprosthetic activity of the right knee with 20 mCi technetium-99m methylene diphosphonate in bone scintigraphy and labelled leukocytes combined with 10 mCi technetium-99m sulphur colloid bone marrow scintigraphy, respectively. Increased activity was remarkable when compared with the corresponding contralateral extremity, which also had undergone a total knee arthroplasty (Figure 1).

In August 2006, after an infectious disease consultation, the patient was started on amphotericin B (1.2 mg/kg/day) 3 days prior to surgery for revision of his right knee. However, during the following week, the patient's BUN and creatinine levels climbed to 86 mg/dl and 3.1 mg/dl, respectively, and the treatment was switched to liposomal amphotericin B (Ambisome; 5 mg/kg/day). The total course of treatment was 6 weeks and the decision to stop treatment was also based on results of bone scintigraphy and labelled leukocytes combined with technetium-99m sulphur colloid bone marrow scintigraphy (Figure 2).

In the middle of August, he underwent removal of the right total knee arthroplasty, irrigation and debridement. At this time, an antibiotic-loaded cement spacer was inserted; since there is no heat-stable antifungal agent for use in cement, teicoplanin was the antibiotic used for protection from a secondary bacterial infection.

Postoperatively the patient's wound healing was uneventful. Two weeks postoperatively, laboratory tests revealed CRP of 3 mg/l (normal range 0–5), BUN 61 mg/dl, creatinine 1.4 mg/dl, and an ESR of 54 mm/h. Four months later, the patient underwent revision of the right total knee arthroplasty. Intraoperative frozen sections were obtained and revealed absence of neutrophils, and culture results showed no evidence of fungal or bacterial infection after a week of incubation. The postoperative period was smooth. The patient has been followed annually with a physical examination and radiographic evaluation and has been free of loosening and asymptomatic during the past 4 y.

Discussion

Aspergillus is a rapidly growing fungus and is often visible in culture within 1 to 3 days of incubation. However, longer periods may be required to see growth if the inoculum is very small. It is an environmental fungus that causes life-threatening infections when improperly treated. *Aspergillus* is widespread in nature. Its spores are easily airborne and we normally breathe in 100 to 200 spores daily. Innate immunity is the main defence against *Aspergillus*. It appears that the onset of the disease depends on the severity of the compromised host defence [10].

Although immunodeficiency and diabetes are amongst the classical risk factors for fungal PJIs, Brooks and Puppato have reported that 46% of the 22 fungal infections known at that time lacked risk factors [11]. Among the documented *Aspergillus*-infected cases, only the patient described by Austin et al. [12] actually was receiving immunosuppressive agents for megaloblastic anaemia, while others including our case were not immunocompromised.

PJIs can be classified as early (those that develop at <3 months after surgery), delayed (at 3–24 months after surgery), or late (at >24 months after surgery) [4]. Early and delayed infections are thought to be due to organisms introduced at the time of surgery, whereas late infections are more likely to be haematogenously acquired. The 4 documented *Aspergillus* spp.-infected cases are evenly split: Patients described by Baumann et al. [13] and Langer et al. [14] had the late type, while our patient and the patient described by Austin et al. [12] had the delayed type PJI. We therefore conclude that PJIs due to *Aspergillus* spp. may be due to

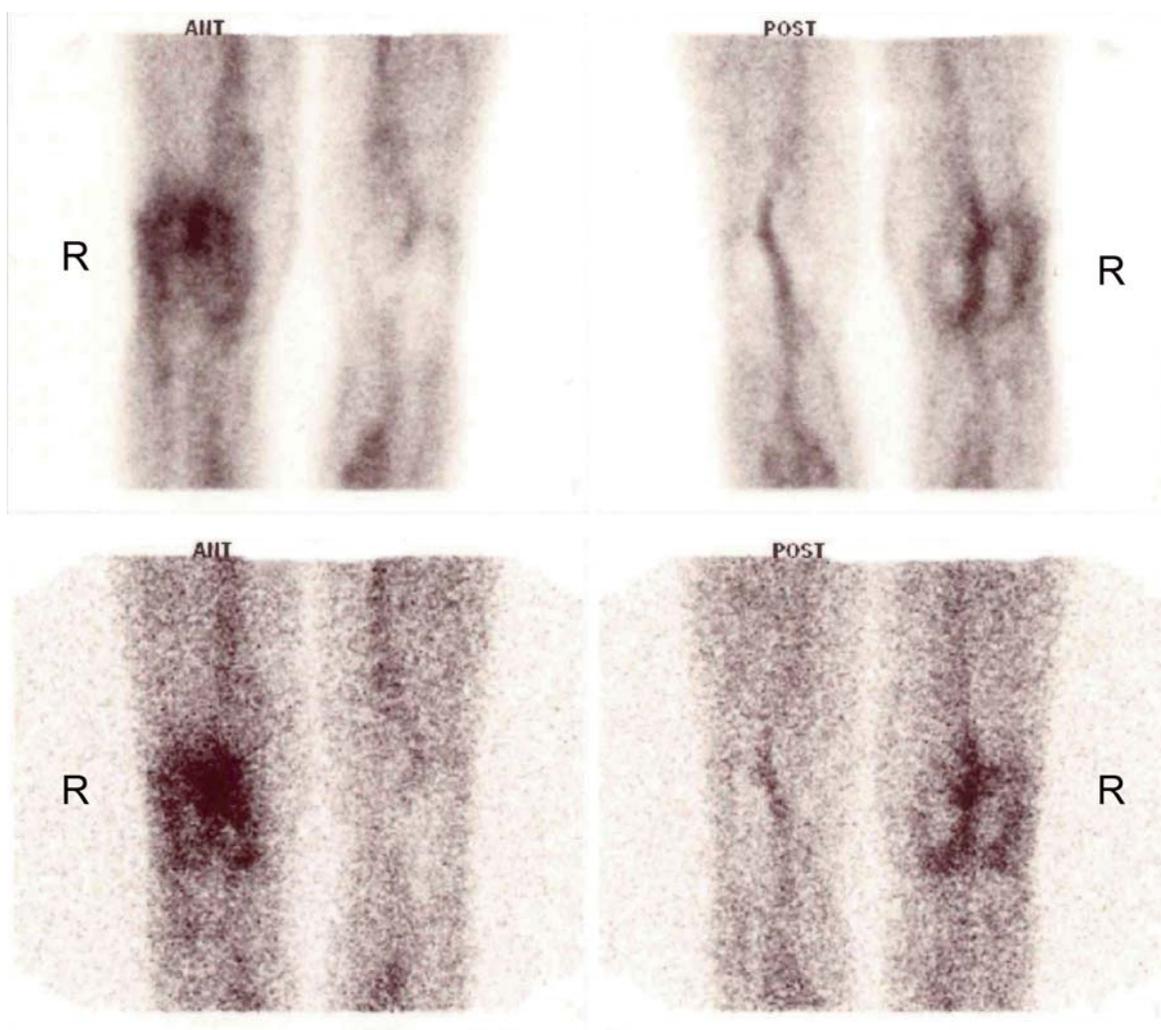


Figure 1. Anterior (left) and posterior (right) labelled leukocyte images of the patient showing increased periprosthetic activity around right total knee replacement with ^{99m}Tc -HMPAO-labelled leukocyte scintigraphy. R, right; Ant, anterior; Post, posterior; images acquired at 2 different time points: 1 h (upper images) and 24 h (lower images).

both organisms introduced at the time of surgery and organisms acquired haematogenously. The patients presented with symptoms of infection following 1 to 4 y of arthroplasty (mean 2.75 y). The average interval between surgery and the appearance of the clinical signs of PJIs due to *Candida* spp. is 21 months and due to *Aspergillus* spp. is 33 months [6].

The available literature on PJIs with fungus consists mainly of case reports and shows *Candida* species to be the most common offending fungal organisms. In 2010 Dutronc et al. reported 62 cases (55 cases from the medical literature and 7 cases from their institute) of prosthetic infections due to *Candida* species. Among the species identified, *Candida albicans* was the most common pathogen to cause prosthetic joint infections (28 cases), followed by *Candida parapsilosis* (18 cases), *Candida glabrata* (8 cases), *Candida tropicalis* (5 cases) and *Candida guilliermondii* (1 case) [6–8,15–20]. So far, there have been 3 reported cases of a total knee arthroplasty infected

with *Aspergillus* species, 2 of which were due to *A. fumigatus* [12,13] and 1 due to *Aspergillus niger* [14]. Patient characteristics are reported in Table I.

Austin et al. described the case of an 80-y-old man who presented 25 months following total knee arthroplasty for excision of a popliteal cyst. The patient underwent an initial surgery for excision of the cyst. The cultures obtained at this surgery grew *A. fumigatus*. Subsequently the patient underwent resection arthroplasty, followed by intravenous administration of amphotericin B for 12 weeks. A follow-up examination at only 12 weeks showed no signs of infection [13]. Baumann et al. successfully treated their case of *A. fumigatus* infection with a 3-stage reimplantation, parenteral amphotericin B, and oral fluconazole suppression. Following an initial surgery of irrigation and debridement with implant resection, antibiotic-impregnated cement was inserted. An additional irrigation, debridement and spacer exchange was performed before

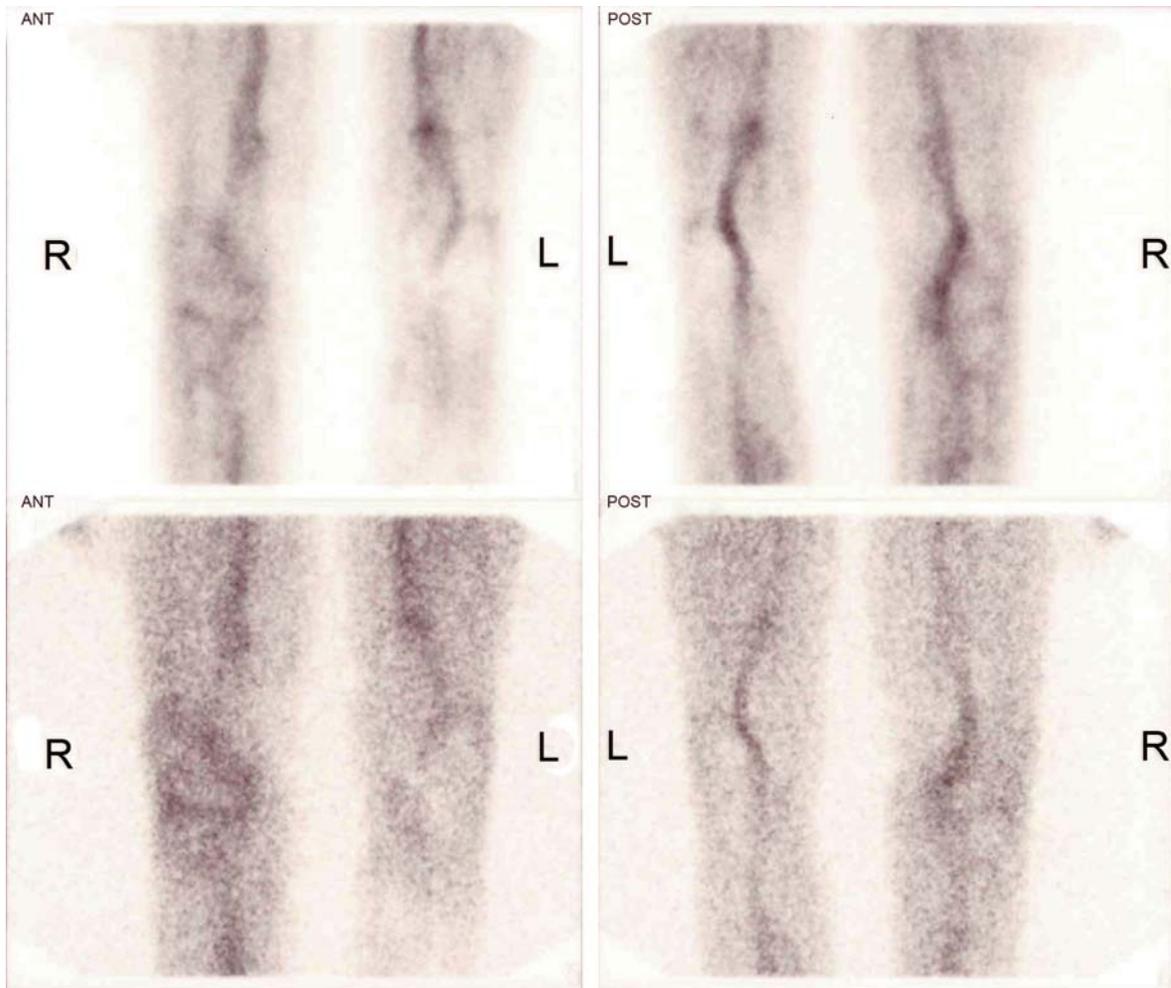


Figure 2. Anterior (left) and posterior (right) labelled leukocyte images of the patient with ^{99m}Tc -HMPAO-labelled leukocyte scintigraphy after 6 weeks of treatment. R, right; L, left; Ant, anterior; Post, posterior; images acquired at 2 different time points: 1 h (upper images) and 24 h (lower images).

reimplantation. Finally, the megaprosthesis was implanted. This treatment was unique in that it was the first successful reimplantation of a fungus-infected megaprosthesis where amputation had been the standard treatment protocol. Five years later, the patient was pain-free and showed no evidence of infection [13]. Langer et al. reported a 65-year-old woman who had undergone a bilateral knee arthroplasty 4 years earlier; she presented with increasing pain and decreasing range of motion of her left knee. She underwent a revision total knee arthroplasty of her left knee and intraoperative cultures grew *A. niger*. The patient was successfully treated with amphotericin B for 6 weeks and was doing well and had no symptoms 12 months after surgery [14]. Our case presented 25 months after a bilateral total knee arthroplasty with pain and swelling of his right knee. He was treated with a 2-stage reimplantation, followed by intravenous administration of amphotericin B for 6 weeks. He was pain-free and showed no evidence of infection at the 4-year follow-up.

All the patients were treated with intravenous amphotericin B (mean 7.5 weeks) and in 1 it was combined with oral fluconazole. All the patients had their prosthesis removed.

The clinical presentation of *Candida* joint infections is often indolent. While fever is observed in rare cases, local signs including pain, erythema and swelling have been described in the majority [6,19,21]. Only 1 of 4 patients with PJIs due to *Aspergillus* spp. had fever with pain and swelling; 2 of them had only pain and swelling of the affected knee and 1 with immunosuppression had no pain but a cyst.

We present a case that was challenging because of the nature of the infecting organism, *A. fumigatus*, in a non-immunocompromised patient. Our patient underwent a 2-stage reimplantation procedure, which is the most common procedure for the treatment of PJIs. Although it is difficult to deduce a management protocol for PJIs due to *Aspergillus* spp. with 4 cases in the last 2 decades, we believe that once a definitive diagnosis is made, a 2-stage reimplantation

Table I. Characteristics of patients with prosthetic joint infections due to *Aspergillus* spp.

Ref. No.	Y ^a	Age	Sex	Immune status	Underlying condition	Prosthesis	Initiation of symptoms following arthroplasty	Pathogen	Treatment			APR upon admission		
									Surgery	Chemotherapy/duration	Outcome and follow-up	Symptoms	ESR (mm/h)	CRP (times normal)
13	1992	80 y	M	Immunosuppressed	Megaloblastic anaemia	Knee	25 months	<i>A. fumigatus</i>	Resection arthroplasty	AmB iv for 12 weeks	Cure; no signs at 12 weeks	Painless popliteal cyst	100	NA
14	2001	27 y	F	Immunocompetent	None	Knee	4 y	<i>A. fumigatus</i>	3-stage reimplantation	AmB iv for 6 weeks followed by Fluc po 8 months	Cure; no signs at 5 y	Pain, swelling, fever, chills	55	12×
15	2003	65 y	F	Immunocompetent	NIDDM	Knee	4 y	<i>A. niger</i>	1-stage reimplantation	AmB iv for 6 weeks	Cure; no signs at 12 months	Pain	31	Normal
Present case	2011	81 y	M	Immunocompetent	None	Knee	1 y	<i>A. fumigatus</i>	2-stage reimplantation	AmB iv for 6 weeks	Cure; no signs at 4 y	Pain, swelling	108	8×

APR, acute phase reactants; ESR, erythrocyte sedimentation rate; CRP, C-reactive protein; M, male; F, female; iv, intravenous; po, per os (oral); AmB, amphotericin B; Fluc, fluconazole; NIDDM, non-insulin-dependent diabetes mellitus; NA, not available.

^aYear published.

procedure involving surgical debridement and antifungal treatment seems a reasonable approach.

Declaration of interest: The authors report no conflicts of interest. The authors alone are responsible for the content and writing of the paper. No support regarding editorial assistance and/or preparation of the article has been received. The corresponding author will be acting as the submission's guarantor. During the study no funding or support of any kind was received from any organization or company.

References

- [1] Coyte PC, Young W, Williams JI. Devolution of hip and knee replacement surgery? *Can J Surg* 1996;39:373–8.
- [2] Darouiche RO. Treatment of infections associated with surgical implants. *N Engl J Med* 2004;350:1422–9.
- [3] Wilson MG, Kelley K, Thornhill TS. Infection as a complication of total knee-replacement arthroplasty. Risk factors and treatment in sixty-seven cases. *J Bone Joint Surg Am* 1990;72: 878–83.
- [4] Zimmerli W, Trampuz A, Ochsner PE. Prosthetic-joint infections. *N Engl J Med* 2004;351:1645–54.
- [5] Kojic EM, Darouiche RO. *Candida* infections of medical devices. *Clin Microbiol Rev* 2004;17:255–67.
- [6] Dutronc H, Dauchy FA, Cazanave C, Rougie C, Lafarie-Castet S, Couprie B, et al. *Candida* prosthetic infections: case series and literature review. *Scand J Infect Dis* 2010;42: 890–5.
- [7] Koch AE. *Candida albicans* infection of a prosthetic knee replacement: a report and review of the literature. *J Rheumatol* 1988;15:362–5.
- [8] Levine M, Rehm SJ, Wilde AH. Infection with *Candida albicans* of a total knee arthroplasty. Case report and review of the literature. *Clin Orthop Relat Res* 1988;(226): 235–9.
- [9] National Committee for Clinical Laboratory Standards. Reference method for broth dilution antifungal susceptibility testing of filamentous fungi. Approved standard M38-A. Wayne, PA, USA: NCCLS; 2002.
- [10] Auberger J, Lass-Flörl C, Ulmer H, Nogler-Semenitz E, Clausen J, Günsilius E, et al. Significant alterations in the epidemiology and treatment outcome of invasive fungal infections in patients with hematological malignancies. *Int J Hematol* 2008;88:508–15.
- [11] Brooks DH, Puppato F. Successful salvage of a primary total knee arthroplasty infected with *Candida parapsilosis*. *J Arthroplasty* 1998;13:707–12.
- [12] Austin KS, Testa NN, Luntz RK, Greene JB, Smiles S. *Aspergillus* infection of total knee arthroplasty presenting as a popliteal cyst. Case report and review of the literature. *J Arthroplasty* 1992;7:311–4.
- [13] Baumann PA, Cunningham B, Patel NS, Finn HA. *Aspergillus fumigatus* infection in a mega prosthetic total knee arthroplasty: salvage by staged reimplantation with 5-year follow-up. *J Arthroplasty* 2001;16:498–503.
- [14] Langer P, Kassim RA, Macari GS, Saleh KJ. *Aspergillus* infection after total knee arthroplasty. *Am J Orthop (Belle Mead NJ)* 2003;32:402–4.
- [15] MacGregor RR, Schimmer BM, Steinberg ME. Results of combined amphotericin B–5-fluorocytosine therapy for prosthetic knee joint infected with *Candida parapsilosis*. *J Rheumatol* 1979;6:451–5.

- [16] Yang SH, Pao JL, Hang YS. Staged reimplantation of total knee arthroplasty after *Candida* infection. *J Arthroplasty* 2001;16:529–32.
- [17] Acikgoz ZC, Sayli U, Avci S, Dogruel H, Gamberzade S. An extremely uncommon infection: *Candida glabrata* arthritis after total knee arthroplasty. *Scand J Infect Dis* 2002;34:394–6.
- [18] Fabry K, Verheyden F, Nelen G. Infection of a total knee prosthesis by *Candida glabrata*: a case report. *Acta Orthop Belg* 2005;71:119–21.
- [19] Lambertus M, Thordarson D, Goetz MB. Fungal prosthetic arthritis: presentation of two cases and review of the literature. *Rev Infect Dis* 1988;10:1038–43.
- [20] Wyman J, McGough R, Limbird R. Fungal infection of a total knee prosthesis: successful treatment using articulating cement spacers and staged reimplantation. *Orthopedics* 2002;25:1391–4; discussion 4.
- [21] 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.