Candida glabrata Prosthetic Hip Infection

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Abstract

We present a case of a 60-year-old Caucasian woman carrying a 2-year-old hip prosthesis infected by *Candida glabrata* dose-dependent susceptible to fluconazole and voriconazole. Resection arthroplasty was performed. Six weeks of caspofungin plus liposomal amphotericin combination therapy achieved joint sterilization and allowed a successfully reimplantation arthroplasty. In addition, we review 9 cases of *C. glabrata* prosthetic joint infection described to date in the literature.

Candidal prosthetic joint infection (PJI) is a rare and potentially devastating complication of total joint arthroplasty. In this case report, we present a case of a 60-year-old Caucasian woman carrying a 2-year-old hip prosthesis infected by *Candida glabrata* dose-dependent susceptible to fluconazole and voriconazole. We also review 9 cases of *C. glabrata* PJI described in the literature.

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The patient provided written informed consent for print and electronic version of this case report.

Case Report

A 60-year-old Caucasian woman, without any significant comorbidity, received a total hip arthroplasty on both hips in 1992 due to a disabling bilateral coxarthrosis. In 2001, at her annual follow-up, a radiograph of the right hip showed the presence of an aseptic loosening of the cemented acetabular component with severe deficit of bone stock (grade 3 American Academy of Orthopaedic Surgeons [AAOS]). In 2002, a right hip revision surgery of the cup was performed. The acetabular bone stock was restored using homologous bone from a donor with impaction bone grafting technique. A Hilock cup (Symbios Orthopédie SA, Yverdon-les-Bain, Switzerland) was implanted with screws; the stem was stable and it was saved.

After 2 years, the patient reported light groin pain during gait. A probable initial mechanical failure of the implant was suspected. Radiograph of the right hip showed radiolucency lines around the cup with mobilization of the obturator hook (Figure A). After 4 months, the patient reported having a fever for the previous 2 months and disabling groin pain at rest and while walking. Other clinical findings were elevated inflammation markers, including C-reactive protein (CRP) 14 mg/L (normal value, <9), erythrocyte sedimentation rate (ESR) 82 mm/h (normal value, <25), fibrinogen 599 mg/dL (normal value, 150-450), which suggested a probable infection. She was admitted to our hospital in March 2005. Arthrocentesis of the right hip joint was performed and the synovial fluid culture resulted positive for *C. glabrata*.

A second revision surgery was performed in that same month and the stem, the cup, and the periacetabular bone were removed with debridement of soft tissues. A temporary gentamicin-loaded spacer was implanted, as it was considered the treatment of choice for the local bone infection (Figure B). At the same time, antifungal therapy was started. The *C. glabrata* isolate showed resistance to itraconazole (minimum inhibitory concentration [MIC], 4 μg/mL), susceptibility dose-dependent to fluconazole (SDD) (MIC, 32 μg/mL), and susceptibility to voriconazole (MIC, 1 μg/mL), caspofungin (MIC, 0.125 μg/ml), amphotericin B (MIC, 0.25 μg/ml), and flucytosine (MIC, 0.03 μg/mL) (Sensititre YeastOne, Trek Diagnostic Systems Ltd,

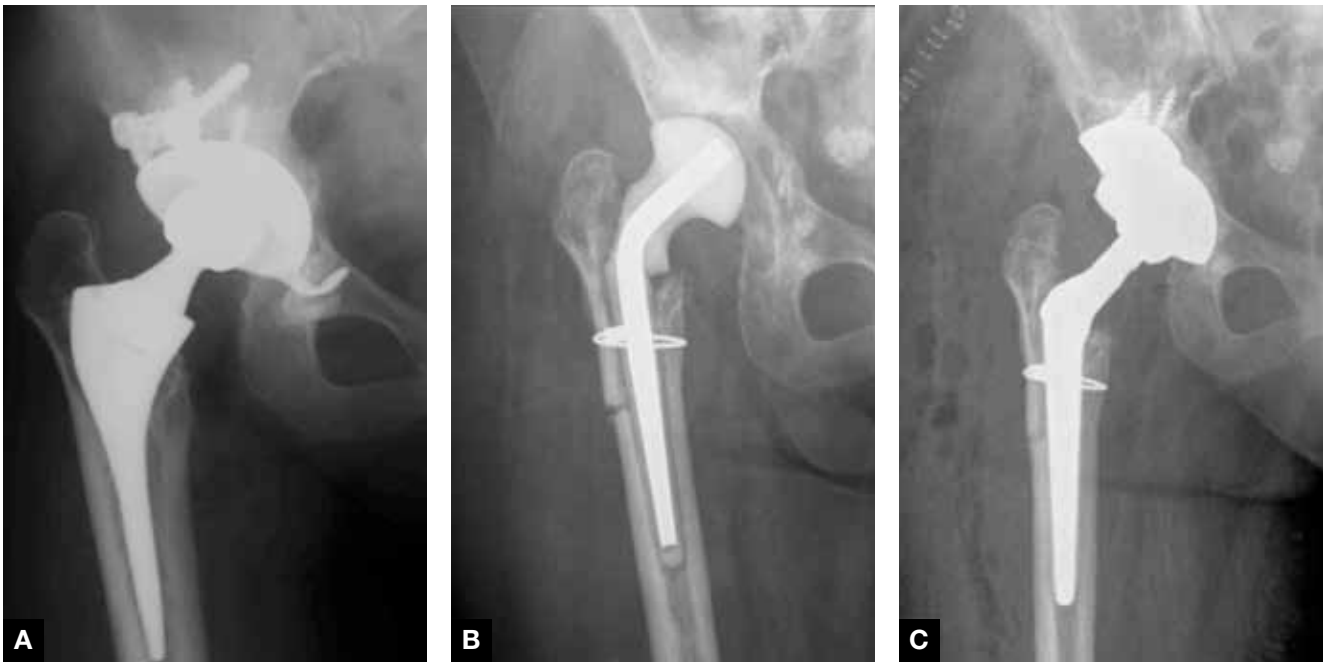

Figure. Radiograph of the right hip: (A) December 2004, radiolucency lines around the cup with mobilization of the obturator hook; (B) March 2005, temporary spacer implanted; and (C) November 2005, new revision surgery performed.

United Kingdom). The need for long-term therapy suggested the patient be treated with voriconazole, considering patient compliance and cost containment (ie, oral vs intravenous therapy, home vs hospitalization). A 12-week course of intravenous (1 week) and oral (11 weeks) voriconazole (200 mg twice daily) was administered (patient weight, 65 kg). Thirty days after the end of antifungal therapy (EOT), inflammation markers were still increased (CRP, 30 mg/L; ESR, 105 mm/h; fibrinogen, 898 mg/dL), labelled white cell scintigraphy (LWCS) results were positive, and a culture of a joint aspiration yielded *C. glabrata*. Therapy was switched to a combination approach with caspofungin (70 mg loading dose, followed by a maintenance dosage of 50 mg once a day) plus liposomal amphotericin B (3 mg/kg, 4 times daily). Moreover, intra-articular administration of deoxycolate amphotericin B 50 mg weekly (6 administrations in total) was added to the intravenous therapy, based on a recent case report of successful treatment of *C. glabrata* arthritis. At the EOT, inflammation markers were reduced, although not in the normal range (CRP, 14 mg/L; ESR, 72 mm/h; fibrinogen, 590 mg/dL), and LWCS performed at 1 month after EOT was normal. Two synovial fluid aspirations performed at 1 and 2 months after EOT were negative as well. In November 2005, a new revision surgery was performed: the severe bone stock deficit (grade 3 AAOS) was restored with homologous bone from donor and impaction bone grafting technique. An acetabular augment (20 mm thickness) with a trabecular metal shell (cluster holes) in tantalum with screws and a Conus stem were implanted (Figure C). In November 2009, at 48 months follow-up, the patient had completely recovered, showed normal inflammation markers (CRP, 7 mg/L; ESR,

Table I. Pharmacokinetic Parameters of Voriconazole

	Week 1 intravenous voriconazole		Weeks 2-12 oral voriconazole
PK parameters	Day 1	Days 2-7	Days 1-14
Peak concentrations* (mg/L)	5.6	3.4 (0.85)	2.13 (1.25)*
6 hours (mg/L)	1.04	1.17 (0.62)	1.47 (0.36)
12 hours (mg/L)	0.8	1.18 (0.57)	1.87 (1.3)
AUC 0-12 hours	33.8	21.6 (9.1)	22.3 (9.8)
Free drug AUC/MIC ratio (%) 24 hours	28.4	17.8	18.8

* 30 minutes after intravenous infusion, or 2 hours after oral intake of drug.
Abbreviations: AUC, area under the curve; MIC, minimum inhibitory concentration.

Table II. Summary of Published Patients With *C. glabrata* Prosthetic Joint Infection

Patient [reference, year of publication]	Age (years), sex	Risk factor(s)	Site of infection	Time from implantation to diagnosis of PJI, months	Symptoms
1 [8, 1983]	69, F	None reported	Hip	26	Pain, swelling
2 [8, 1997]	62, F	*C. glabrata* urinary tract infection, diabetes	Hip	60	Pain (of long duration, but months not exactly reported)
3 [8, 1998]	75, F	ICU hospitalization 3 months before symptoms	Knee	84	Pain, swelling
4 [4, 2001]	65, F	None reported	Hip	60	Pain (12 months after THA); revision of the stem; pain (48 months after stem revision)
5 [8, 2002]	70, F	None reported	Knee	9	Severe pain, swelling
6 [8, 2004]	42, F	Lupus treated with chronic steroids, C. *glabrata* sepsis and urinary tract infection	Knee	252	Local signs of infection
7 [10, 2005]	73, NR	Diabetis	Hip	192	Pain
8 [9, 2008]	72, NR	Diabetis, corticoid-treated rheumatoid arthritis	Knee	NR	Pain
9 [PR, 2012]	60, F	None	Hip	28	Pain, fever (of 4 months duration)

Abbreviations: ICU, intensive care unit; NR, not reported; THA, total hip arthroplasty; PR, Present Report.

22 mm/h; fibrinogen, 375 mg/dL), and the joint infections signs and symptoms had completely disappeared.

Taking into account the known nonlinear pharmacokinetic profile of voriconazole and the MIC value at the upper limit of susceptibility, we collected blood samples in order to determine voriconazole plasma concentration during both intravenous and oral treatment. Voriconazole plasma samples were collected in the 12-hour period following either intravenous or oral administration. The samples were collected daily in the week of the intravenous administration and for the first 2 weeks during the oral administration period. An aliquot (0.5 mL) of plasma samples was added to acetonitrile (0.8 mL), then the mixture was vortex mixed briefly and centrifuged at 1200×*g* for 5 min. The supernatant was transferred to autosampler vial and 0.1 mL injected into the high-performance liquid chromatography (HPLC) system. Voriconazole concentrations were determined in HPLC, with UV detector set at 255 nm, an analytical column C18, 5 µm, 150×4.6 mm

Reported suceptibility testing for the *Candida glabrata* isolate (MIC, mg/mL, when available)	Therapy	Outcome	Duration of follow-up, months
NR	Removal; AmpB irrigation of joint cavity for 7 days	Cure	NR
AmpB = 0.25 5FC = 0.125 FLU = 32 ITR = 1	Removal and reimplantation; 5FC for 4 weeks; 5FC+AmpB for 12 days (stopped for nephrotoxicity); then 5FC+ITR for 6 weeks	Cure	16
AmpB = S ITR = S FLU = R	AmpB + ITR or and ia; failure; removal and reimplantation with AmpB (200 mg)-impregnated bone-cement; AmpB iv for 1 week and ia for 48 hours + ITR or for 8 weeks	Cure	48
AmpB = S 5FC = S FLU = R ITR = R	Removal; AmpB iv (0.75-1 mg/kg/day) + 5FC iv (200 mg/kg/day) for 6 weeks; reimplantation	Cure	24
AmpB = S 5FC = S FLU = S ITR = S	Debridement, 2-stage exchange with ceftriaxone 6 weeks; Recurrence (6 months after reimplant); arthrodesis with external fixator; FLU (200 mg qd) os (duration not reported)	Cure	7
NR	Removal and placement of antibiotic (VAN+AnpB) spacer; VOR for two months + ia AmpB; repeat debridement + placement of new spacer; recurrence (after 2 months); new debridement e new antibiotic spacer; recurrence; 1 month later above-knee amputation	Amputation	6
FLU = 24 ITR = R	Removal; spacer insertion; spacer removal; LAmp (300 mg qd) for 37 days; extensive debriment; AmpB (2500 mg of total dose); CAS iv (70 mg than 50 mg qd) for 3 weeks	Cure	36
CAS = 0.380 5FC = 0.006 FLU = 4	CAS iv (70 mg then 50 mg qd) + 5FC iv (2,5 g/12h) for 5 weeks (started 2 weeks before removal); removal; arthrodesis (3 weeks later); FLU or (400 mg qd) + 5FC or (5g qd) for 4 months	Cure	15
AmpB = 0.25 5FC = 0.03 FLU = 32 ITR = 4 VOR = 1 CAS = 0.125	Removal; 2 weeks of VOR iv (200 mg bid) + 10 weeks of VOR or (200 mg bid); failure; 6 weeks of CAS (70 mg loading does; 50 mg qd) + LAmp (3 mg/kg qd) + AmpB (50 mg ia weekly); reimplantation	Cure	48

Abbreviations: 5FC, 5-flucytosine; AmpB, amphotericin B; bid: twice a day; FLU, Fluconazole; ia, intra-articular; ITR, itraconazole; iv, intravenous; LAmp, liposomal amphotericin B; NR, not reported; or, oral; PR, present report; qd: once a day; R, resistant; S, susceptible; VAN, vancomycin; VOR, voriconazole.

with a 10×3.2 mm guard cartridge packed with the same material and a mobile phase of acetonitrile-ammonium phosphate buffer (pH 6.0; 0.04 M) (1:1 v/v), with a flow rate of 1 mL min^{-1}. The intra-run accuracy and precision in plasma were assessed by performing replicate analyses of samples fortified with voriconazole at 0.05, 0.1, 0.2, 2, and 10 μg mL^{-1}. Where 0.05 and 0.1 μg mL^{-1} samples were assayed, the calibration line was extended with 0.05 and 0.1 μg mL^{-1} standards as appropriate to avoid extrapolation. The inter-run accuracy and precision were determined from the back calculated concentrations for the standards used to construct 4 different calibration curves in separate runs.[1] Voriconazole plasma concentrations are reported in Table I. Peak concentrations were similar to those observed in both patients and volunteers.[2] Plasma levels at 6 or 12 hours after dose were relatively low and always lower than 2 mg/L. Free drug area under the curve (AUC)/MIC ratio ranged from 17.8 and 28.4, both after intravenous

or oral dose and, with the exclusion of the loading dose, were always lower than 20.

Discussion

PJI is a well-known complication of total joint arthroplasty. Although candidal PJI is rare, accounting for approximately less than 1% of all PJI, it is a potentially devastating complication. The exact mechanism of prosthetic joint *Candida* species infections is not clear. It has been suggested that a possible explanation might be the direct inoculation during surgery. However, there is often a long interval between surgery and the occurrence of *Candida* species. PJI, as in our patient, suggests the possibility of a hematogenous route as a result of an unrecognized candidemia rather than a direct bone contact with the fungus.

To date, only 49 cases of candidal PJI have been reported and only 8 due to *C. glabrata*. Of these 49 cases, only 13 candidal PJI (6 *Candida albicans*, 4 *Candida parapsilosis*, 2 *Candida tropicalis, 1 C. glabrata*) were treated with delayed reimplantation arthroplasty, with wide duration range (2 weeks-11 months) of antifungal therapy and a cure rate of 84.6% (11/13).[3-6] Recent treatment guidelines for candidiasis advise use of resection arthroplasty with antifungal therapy and suggest that, after successful therapy, a new prosthesis may be implanted.[7] However, there is still a lack of standardized treatment of candidal PJI, as we can see in the 8 cases due to *C. glabrata,* that have been treated with several and different therapeutic approaches (Table II).[4,8-10]

Although the cure of infection was achieved in all but 1 case, 1 case needed above-knee amputation, 2 patients underwent an intervention for arthrodesis, and 2 patients remained without prosthesis. Reimplantation of a new prosthesis was only obtained in 3 cases. In all 3 cases, a combination therapy of 2 systemic antifungal drugs was utilized. Of these cases, only one was successfully treated with a 2-stage revision of the arthroplasty, in association with 6 weeks of combination antifungal therapy based on amphotericin B and flucytosine.

In our case, *C. glabrata* isolate showed a voriconazole MIC of 1 μg/mL, which coincided with the suggested MIC breakpoint for voriconazole in vitro susceptibility.[11] This was determined with the Sensititre YeastOne system (Trek Diagnostic Systems Ltd), which seems to be a reliable commercial tool.[12] Nevertheless, it is known that breakpoints were arbitrarily chosen in order to determine the percentage of susceptible isolates and it is possible that the true in vivo susceptibility cut-off could be lower or higher than 1 μg/mL. In our patient, the therapy did not clear the hip infection, despite change of the yeast isolate in vitro susceptibility after a 12-week voriconazole therapy, which excludes the emergence of an induced drug resistance. Certainly, the in vitro susceptibility is not yet a reliable predictor of a clinical successful outcome, since tissue penetration of the drug and host factors play an important role. Voriconazole has been used in bone and joint infections, though the penetration of this azole derivative into synovial fluid and bone tissues has been reported only recently in a 83-year-old woman with left knee arthritis due to *Aspergillus fumigatus*.[13] However, the pharmacokinetics of voriconazole in volunteers and patients has shown that this compound exhibits a nonlinear pharmacokinetic profile. This phenomenon is mainly due to voriconazole metabolism which is mostly mediated through *CYP2C19* with allelic polymorphisms.[2] Azole derivatives are concentration independent drugs and, from a pharmacokinetic/pharmacodynamic point of view, they need to maintain a free-drug AUC/MIC ratio of almost 25-30 for successful treatment. Moreover, Smith and colleagues[14] recently demonstrated a true relationship between disease progression and voriconazole concentration in 28 patients who underwent voriconazole monitoring, thus suggesting that serum concentrations less than 2.05 mg/L are related with disease progression. It is, however, been recently shown that the intracellular activity of voriconazole against *Candida* species depends on both concentration—maximal intracellular anticandidal activity at 3.5-5 X MIC—and on time of exposure. In our patient, voriconazole concentrations ranged from 0.8 to 3.4 mg/L, with the exclusion of C_{max} after the loading intravenous dose, while within and trough concentrations were always lower than 2 mg/L. Moreover, the free-drug AUC/MIC ratio was always lower than 20. Therefore, our pharmacokinetic findings may well explain the treatment failure observed in our patient, suggesting the need for careful monitoring of pharmacokinetic parameters during treatment with voriconazole. In the reported case, data on voriconazole plasma concentration were available only after its clinical use, as at that time voriconazole plasma concentration drug monitoring was not routinely performed, as actually suggested, and did not allow dose adjustment.[15]

Due to the unsuccessful outcome of the voriconazole treatment, we considered the option of combining a cell wall active agent (caspofungin) with a membrane active drug (amphotericin B). This combination has shown no antagonistic interaction in vitro and an additive or synergic effect in a murine candidemia model. Moreover, caspofungin has shown potent in vitro activity also against *Candida* species isolates displaying different mechanisms of azole resistance, and a maintained activity against *Candida* species Biofilms.[16] With only 6 weeks of caspofungin plus liposomal amphotericin B treatment, we achieved the normalization of LWCS and a sterile synovial fluid culture.

This case report shows once more that *Candida* species PJI is still very difficult to treat and is a potentially devastating complication. Moreover, in the absence of standardized clinical and evidence-based guidelines, our case underlines the need of a proper antifungal therapy and of a strict plasma concentrations drug monitoring, especially when an azole antifungal agent is used.

Conclusion

To our knowledge, this is the first case of *C. glabrata* PJI successfully treated with delayed reimplantion arthroplasty after 6 weeks of caspofungin plus liposomal amphotericin B combination therapy proving to be safe, effective, and very rapid in clearing the infection.

Authors' Disclosure Statement

The authors report no actual or potential conflict of interest in relation to this article.

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