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Azole-resistant *Candida albicans* prosthetic joint infection treated with prolonged administration of anidulafungin and two-stage exchange with implant of a mega-prosthesis

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Fungal prosthetic joint infection (PJI) is a rare but severe complication of arthroplasty. We report a case of PJI due to azole-resistant *Candida albicans* successfully treated with combination of prolonged administration of anidulafungin and two-stage joint exchange with insertion of a mega-prosthesis.

Keywords: Anidulafungin, Prosthetic joint infection, Mega-prosthesis, *Candida albicans*

Prosthetic joint infection (PJI) is a dramatic complication of arthroplasty, most frequently due to *Staphylococcus aureus* and coagulase-negative staphylococci.¹ Fungal infections are sporadically described (1% of all PJI) and can be observed also in patients without risk factors for invasive mycoses.^{2,3} This rare complication requires a prolonged treatment and the final outcome is frequently poor.⁴

We report a case of PJI due to azole resistant *Candida albicans* (*C.albicans*) successfully treated with combination of anidulafungin and two stage joint exchange with insertion of a mega-prosthesis.

Case report

A 68-year-old diabetic woman with hip arthroplasty was evaluated in our centre on April 2014 for a two-year history of progressive pain. Clinical history showed a right hip arthroplasty performed on October 2012 in another centre and a traumatic periprosthetic fracture treated with locked plate fixation on November 2012 (Fig. 1(a)). Six months before admission in our centre, a sinus tract, highly suggestive for PJI was observed. As a consequence, she was treated empirically with teicoplanin and ciprofloxacin. Low-dose fluconazole (100 mg/day) was added because of growth of *C.albicans* from a fistula swab. At our first observation, the patient was afebrile, in good clinical

condition, slightly overweight (Body Mass Index: 29). She was bedridden because of severe hip pain. C-reactive protein (CRP) and erythrocyte sedimentation rate (ESR) were in the normal range.

At this time, we decided to perform a 'two stage revision' with the removal of prosthetic joint and other hardware, extensive debridement and implant of a long femoral stem spacer to preserve the distal femur and to maintain the knee (Fig. 1(b)). Three intraoperative cultures performed during removal of the infected prosthesis, according to international recommendations,⁵ yielded a pure culture of *C.albicans* and the susceptibility tests (Sensititre, Thermo Fisher Scientific) showed high minimal inhibitory concentrations (MIC) for triazoles (fluconazole >256 mg/L, voriconazole 8 mg/L), while MIC for echinocandins was within the susceptibility range (anidulafungin MIC 0.015 mg/L).⁶ The patient was treated with anidulafungin (first day 200 mg, then 100 mg q24 h intravenously) for six weeks, but a new fistula became evident at the distal part of the thigh one month after the end of treatment. A [18F]-2-deoxy-D-glucose positron emission tomography with computerized tomography (PET/CT scan) showed abnormal uptake in distal femur. Considering the persistence of infection, anidulafungin was prescribed again and a spacer revision with knee resection was performed. At this time, a custom made total femoral spacer with acetabular and tibial anchoring was inserted (Fig. 1(c) and (d)). Once again *Candida albicans* grew from intraoperative

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Figure 1 (a, b): hip radiograph at admission in our centre; (c, d): custom-made long spacer; (e, f): final result after insertion of a mega-prosthesis.

samples of the resected knee. Anidulafungin concentrations were evaluated in plasma and bone biopsy, and 4 h before infusion resulted in: plasma 3.41 mg/L and bone 0.38 mg/L (A. Novelli, Institute of Pharmacology, University of Florence).^{6,7} Liposomal amphotericin B was associated to anidulafungin, but the treatment was stopped immediately because of a severe adverse event occurring during the first infusion. Anidulafungin treatment was prolonged for another six weeks at the usual dosage and the patient was followed up for one further month after the end of treatment. No relapse was observed but after two surgical procedures and the implant of a custom-made long spacer, the patient presented severe bone stock deficiency. For this reason, at replacement, a mega-prosthesis inserted from hip to knee, usually adopted for treatment of bone cancer (Fig. 1(e) and (f)) was inserted. Three new intraoperative cultures performed at replacement were negative. Anidulafungin was administered for other two weeks after surgery. Follow up after the end of treatment showed CRP and ESR persistently within the normal range, a PET-CT scan was negative six months after anidulafungin withdrawal and 14 months after mega-prosthesis insertion, the patient was free from infection and able to walk with crutches.

Comments

We have described a successful treatment of PJI due to fluconazole-resistant *C. albicans* with long-term use of anidulafungin and implantation of a mega-prosthesis after two radical revisions. Fungal infections are uncommon cause of PJI, sometimes described in polymicrobial infections.^{2,3,8} The pathogenesis of this rare infection is difficult to identify in our patient. A possibility is haematogenous dissemination in a patient with risk factors (diabetes, overweight, antibiotic treatment), but candidemia was never documented.⁹ Another possibility is intraoperative fungal contamination during treatment for the traumatic fracture, but this hypothesis was not even proved. Indeed, *C. albicans* was initially cultured from a fistula in another centre, but it was considered as a contaminant and treated with low-dose fluconazole.¹⁰ Bone concentration of fluconazole is poor, so high doses would be needed to achieve effective concentrations and the very low dose administered to this patient was probably the cause of resistance.¹¹ Amphotericin B and voriconazole

have the best bone tissue concentrations, but their use was not feasible because of the high MIC for voriconazole and the adverse event to liposomal amphotericin B infusion.¹¹ To the best of our knowledge, no specific echinocandin tissue distribution studies have been done in humans and anidulafungin has not been studied in osteomyelitis. In spite of this, in an *in vivo* preclinical study in neonatal rats¹², anidulafungin concentrations in bone were comparable to those in plasma regardless of dosing duration, with similar peak (C_{max}) concentration and area under the concentration – time curve (AUC) for both plasma and bone, even if peak in bone was later than that obtained in plasma.¹² Anidulafungin was chosen among the echinocandins because of the availability of these data even if derived from experimental models. We did not evaluate the peak/MIC ratio, even if this is the pharmacokinetic/pharmacodynamic index that could better describe echinocandin efficacy.¹³ Anyway, we analyzed plasma and bone concentrations and found a bone–tissue concentration at trough of near 1/10 of that observed in plasma, but still 25 times higher than the MIC of the isolated strain. Also, slime production by *C. albicans* could be a potential cause of failure since it increases *Candida* adhesion to the prosthetic device. Anidulafungin is effective against slime producing *Candida* strains, even if higher anidulafungin concentrations are needed for treatment.¹⁴ In spite of the low bone concentrations, treatment was effective (negative cultures at replacement).¹⁵

In this severe PJI, we adopted a two-stage exchange strategy because of the high risk of relapse.^{16,17} Probably, the accurate debridement during two surgical procedures had an important role for recovery also if we have employed a custom-made spacer without antifungal addition in contrast with other reports that suggest to add amphotericin B in spacer.¹⁸ The second radical debridement caused bone stock deficiency that required employment of a mega-prosthesis. This device is frequently used in treatment of bone cancer, but not in PJI because of the high risk of infection relapse. However, the strategy of radical debridement and long-term employment of an (*in vitro*) effective drug with a reasonable bone penetration (in absence of the possibility of administering other drugs with more favourable kinetics) resulted effective. We have documented the absence of relapse of infection 14 months after anidulafungin withdrawal, and acceptable functional recovery.

Our experience strictly underlines the need to consider fungal isolations carefully in patients with PJI and to employ a prolonged antifungal treatment at full doses. The most recent guidelines for treatment of invasive *Candida* infection indicate antifungal and prosthesis revision as cornerstone for treatment of *Candida* PJI, but underlines also the possibility of arthrodesis or long-term antifungal suppressive therapy in failures.¹⁹ Our case report suggests that, if adequate antifungal treatment is prescribed, even in presence of repeated failures and stock bone deficit, a mega-prosthesis could be used to improve patients' quality of life.

Contributors GC was responsible for treatment decisions, paper conception and report and result analysis. LC was responsible for clinical follow up and data collection. MB was responsible for clinical follow up and data collection. GR was responsible for treatment evaluation and result analysis. AR was responsible for microbiological studies and data collection. CS was responsible for orthopaedic treatment decisions and data collection. GB was responsible for orthopaedic treatment decisions and results analysis.

References

- 1 Tande AJ, Patel R. Prosthetic joint infection. *Clin Microbiol Rev.* 2014;27(2):302–45.
- 2 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(11–12):890–5.
- 3 Jakobs O, Schoof B, Klatte TO, Schmidl S, Fensky F, Guenther D, et al. Fungal periprosthetic joint infection in total knee arthroplasty: a systematic review. *Orthop Rev (Pavia).* 2015;7(1):5623. doi: <http://dx.doi.org/10.4081/or.2015.5623>.
- 4 Ueng SW, Lee CY, Hu CC, Hsieh PH, Chang Y. What is the success of treatment of hip and knee candidal periprosthetic joint infection? *Clin Orthop Relat Res.* 2013;471(9):3002–9.
- 5 Osmon DR, Berbari EF, Berendt AR, Lew D, Zimmerli W, Steckelberg JM, et al. Executive summary: diagnosis and management of prosthetic joint infection: clinical practice guidelines by the Infectious Diseases Society of America. *Clin Infect Dis.* 2013;56(1):1–10.
- 6 Espinel-Ingroff A, Alvarez-Fernandez M, Cantón E, Carver PL, Chen SC, Eschenauer G, et al. Multicenter study of epidemiological cutoff values and detection of resistance in *Candida* spp. to anidulafungin, caspofungin, and micafungin using the Sensititre YeastOne colorimetric method. *Antimicrob Agents Chemother.* 2015;59(11):6725–32.
- 7 Mazzei T, Novelli A. Pharmacological properties of antifungal drugs with a focus on anidulafungin. *Drugs.* 2009;69(Suppl 1):79–90.
- 8 Marculescu CE, Cantey JR. Polymicrobial prosthetic joint infections: risk factors and outcome. *Clin Orthop Relat Res.* 2008;466(6):1397–404.
- 9 Phelan DM, Osmon DR, Keating MR, Hanssen AD. Delayed reimplantation arthroplasty for candidal prosthetic joint infection: a report of 4 cases and review of the literature. *Clin Infect Dis.* 2002;34(7):930–8.
- 10 Reddy KJ, Shah JD, Kale RV, Reddy TJ. Fungal prosthetic joint infection after total knee arthroplasty. *Indian J Orthop.* 2013;47(5):526–9.
- 11 Felton T, Troke PF, Hope WW. Tissue penetration of antifungal agents. *Clin Microbiol Rev.* 2014;27(1):68–88.
- 12 Ripp SL, Aram JA, Bowman CJ, Chmielewski G, Conte U, Cross DM, et al. Tissue distribution of anidulafungin in neonatal rats. *Birth Defects Res B Dev Reprod Toxicol.* 2012;95(1):89–94.
- 13 Theuretzbacher U. Pharmacokinetics/pharmacodynamics of echinocandins. *Eur J Clin Microbiol Infect Dis.* 2004;23(11):805–12.
- 14 Katragkou A, Chatzimoschou A, Simitsopoulou M, Dalakiouridou M, Diza-Mataftsi E, Tsantali C, Roilides E. Differential activities of newer antifungal agents against *Candida albicans* and *Candida parapsilosis* biofilms. *Antimicrob Agents Chemother.* 2008;52(1):357–60.
- 15 Liu P. Population pharmacokinetic-pharmacodynamic analysis of anidulafungin in adult patients with fungal infections. *Antimicrob Agents Chemother.* 2013;57(1):466–74.
- 16 Kuiper JW, van den Bekerom MP, van der Stappen J, Nolte PA, Colen S. 2-stage revision recommended for treatment of fungal hip and knee prosthetic joint infections. *Acta Orthop.* 2013;84(6):517–23.
- 17 Wang QJ, Shen H, Zhang XL, Jiang Y, Wang Q, Chen YS, Shao JJ. Staged reimplantation for the treatment of fungal peri-prosthetic joint infection following primary total knee arthroplasty. *Orthop Traumatol Surg Res.* 2015;101(2):151–6.
- 18 Deelstra JJ, Neut D, Jutte PC. Successful treatment of *Candida albicans*-infected total hip prosthesis with staged procedure using an antifungal-loaded cement spacer. *J Arthroplasty.* 2013;28(2):374.e5–8.
- 19 Pappas PG, Kauffman CA, Andes DR, Clancy CJ, Marr KA, Ostrosky-Zeichner L, et al. Clinical practice guideline for the management of candidiasis: 2016 update by the Infectious Diseases Society of America. *Clin Infect Dis.* 2016;62(4):e1–50.