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Review

Candida Prosthetic Joint Infection. A Review of Treatment Methods

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Abstract

Fungal microorganisms are still a rare cause of bone and joint infections. We report a new case of knee prosthetic joint infection due to *Candida albicans* in a patient with a previous two-stage right knee arthroplasty for septic arthritis due to *S. epidermidis* occurred several months ago. Moreover, the treatment in 76 cases of *Candida* prosthetic joint infection has been discussed. Forty patients were female and mean age at diagnosis was 65.7 (± SD 18) yrs. No risk factors for candidal infection were found in 25 patients. Infection site was the knee in 38 patients and hip in 36; pain was present in 44 patients and swelling in 24. The most frequent species was *C. albicans*, followed by *C. parapsilosis*. Eleven patients were only treated with antifungal drugs being the outcome favourable in all of them. Two-stage exchange arthroplasty was performed in 30 patients, and resection arthroplasty in other 30; in three patients one-stage exchange arthroplasty was done. A favourable outcome was found in 58 patients after antifungal plus surgical treatment, in 11 after antifungal treatment alone and in one after surgery alone. The type of treatment is still not clearly defined and an algorithm for treatment in fungal PJI should be established, but various types of surgical procedures may be applied.

Key words: Prosthetic joint infection, *Candida albicans*, arthroplasty, infection, antifungal drugs, surgical treatment

Introduction

Prosthetic joint infection (PJI) involves the joint prosthesis and contiguous tissue and is one of the main reasons for total arthroplasty failure [1, 2]. A wide range of microorganisms may cause PJI, most often Gram-positive bacteria, especially staphylococcal species, and Gram-negative pathogens [3]. However, other microorganisms can also be responsible for PJI, including fungi, particularly *Candida* species. PJI due to *Candida* is rare and represents a therapeutic challenge because no specific guidelines have been already established and published case reports vary widely in therapeutic approach [4]. Currently, the *gold standard* for treatment consists in a two-stage revision surgery [4, 5], although it is doubtful whether multiple procedures are able to provide any improvements and it is also unknown if other techniques such as one-stage exchange may be successful.

Here, we describe one patient seen at the Orthopaedics and Trauma Department of the Hospital Universitario Virgen de las Nieves (Granada, Spain) with PJI due to *C. albicans* which is being treated with antifungal drugs alone. Moreover, we have reviewed the medical literature searching case reports with *Candida* PJI discussing about the treatment methods applied.

Case Report

A 66-year-old man had a right knee arthroplasty due to osteoarthritis suffered for several years. In January 2015, the patient underwent a two-stage right knee arthroplasty for septic arthritis due to *S. epidermidis,* as well as treatment with vancomycin + gentamycin. He was immunocompromised due to a splenectomy performed several years ago. In July 2016, the patient was attended at the Emergency Department of our Hospital due to pain, inflammation and joint leak for two weeks. The physical examination revealed inflammatory signs and swelling on the knee. The complete blood count, chemical profile and urinalysis were normal, except for a C-reactive protein (CRP) of 100 mg/L. A joint fluid (JF) was drawn by puncture from the affected knee and sent to the microbiology laboratory. The sample was inoculated after centrifugation in aerobic and anaerobic blood agar (BD Columbia Agar 5% Sheepblood®, Becton Dickinson), chocolate agar (BD Choco Agar, Becton Dickinson) and thioglycollate broth (BD™ Fluid Thioglycollate Medium), all incubated at 37º C. Previously, 1 mL of the JF was inoculated into an aerobic blood culture bottle (BACTEC, 9240 BD, Becton Dickinson, Franklin Lakes, NJ, USA), being positive after 24 hours of incubation. Pathogen growth was observed on aerobic blood agar and chocolate agar. Identification of *C. albicans* and susceptibility to this strain were then tested using the Vitek system (BioMérieux, Mercy L'Etoile, France) as well as mass spectrometry (Bruker Biotyper, Billerica, MA, USA). The isolate was susceptible to anidulafungin (0.015 µg/ml), micafungin (<0.008 µg/ml) caspofungin (0.06 µg/ml), voriconazole (<0.008 µg/ml), itraconazole (0,03 µg/ml) fluconazole (0,125 µg/ml), and amphotericin B (1 µg/ml). Breakpoints from CLSI were used for the majority of antifungal drugs, but only from EUCAST for amphotericin B [6, 7]. No blood cultures were taken at this stage. The patient rejected a prosthesis exchange, so a surgical procedure was then done with local debridement of the lesion, and five intraoperative periprosthetic tissue samples were taken from different locations, following recommendations of Kamme and Lindberg [8]. In the laboratory, each sample (1 cm^2) was placed in 3 ml of sterile saline solution and vortexed for 30 seconds. Then, the sample was inoculated in aerobic and anaerobic blood agar (BD Columbia Agar 5% Sheepblood®, Becton Dickinson), chocolate agar (BD Choco Agar, Becton Dickinson) and thioglycolate broth (BD™ Fluid Thioglycollate Medium, Becton Dickinson), all incubated at 37º C., and chromogenic candida agar (CandiSelect ™, Bio-Rad, Redmond, WA, USA) incubated at 30º C. After 18 hours of incubation, microorganism growth was again observed and further identified as *C. albicans*.

Treatment with caspofungin (50 mg/day) was administered for 14 days, and the patient was then discharged under oral suppressive treatment with fluconazole (200 mg/12 h.) for 6 months. At 2 months of follow-up, the patient remained clinically stable, and laboratory findings were normal. At the moment, the patient has rejected prosthesis reimplantation and is currently waiting for a 6 months of antifungal treatment.

Literature Review

We describe one patient recently seen at the Orthopaedics and Trauma Department of the Hospital Universitario Virgen de las Nieves (Granada, Spain) with PJI due to *C. albicans*.

Using the key words "fungal prosthetic joint infection" and "candida prosthetic joint infection" we searched MEDLINE (National Library of Medicine, Bethesda, MD), Web of Science, CINAHL, and Cochrane systematic review databases for case reports of this condition. We also checked the references cited in the papers for additional case reports published before 1966.

We traced 75 cases caused by *Candida* species and described in sufficient detail. These cases, along with our patient, are the basis of the present report. Among others, data on treatment, outcome and follow-up were recorded. A patient was considered to have *Candida* infection and was then included when a positive preoperative aspiration culture and/or a positive intraoperative culture were obtained. We did not include cases with *Candida* infection accompanied by another pathogen or cases with insufficient details for comparisons (clinical and laboratory data).

The basis for this review was recently published [9], but we have added three new cases of *Candida* PJI. Table 1 summarizes the treatment, outcome and follow-up of all cases here reviewed.

General Characteristics

There were 40 (52.6%) women, while the sex was not reported in two patients. The mean age of patients was 65.7 (± SD 18) yrs (range 35-93 yrs). Thirty-five cases were from the USA [10-33], 10 from Taiwan [34-36], six from the United Kingdom [37-41], six from Germany [42], four from France [43-45], three from Italy [46-48], two each from Japan [49, 50] and Spain [9, and present report], and one each from China [51], India [52], Slovenia [53], Belgium [54], Turkey [55], Canada [56], Malaysia [57] and Sweden [58]. No risk factors for candidal infection were found in 25 patients (32.8%). The joint involved was the knee in 38 (50%), the hip in 36 (47.3%) and the shoulder in two

cases. Pain was reported by 44 (57.8%) patients, and the second most frequent symptom was swelling in 24 (31.5%) patients. Symptoms were not reported for 18 (23.6%) patients.

The most frequently isolated *Candida* species was *C. albicans*, found in 36 (47.3%), followed by *C. parapsilosis* in 17 (22.3%), *C. glabrata* in 12 (15.7%) and *C. tropicalis* in 8 (10.5%), with infection by both *C. albicans* and *C. glabrata* in one patient [40]. *Candida* species were diagnosed by culture of joint fluid (JF) aspirate in 33 cases (43.4%), culture of intraoperative sample (IoS) in 18 (23.6%) and culture of both JF and IoS samples in 19 (25%). Blood cultures were taken only in eight (10.5%) patients, and were positive for *Candida* in four of these (50%).

Table 1. Treatment, outcome and follow-up of 76 patients with *Candida* species PJI.

Reference/ author	Treatment Antifungal treatment	Surgical treatment	Outcome	Follow-up (months)
51/Zhu Y	Amphotericin B Voriconazole	NR	Cure	3
52/Reddy KJ	Fluconazole Amphotericin B ICS	TEA	Cure	24
46/Artiaco S	Fluconazole Miconazole	Drainage of abscess	Cure	12
37/Lidder S	Amphotericin B	TEA	Cure	24
34/Ueng SWN	Fluconazole Amphotericin B ICS	TEA	Cure	NR
34/Ueng SWN	Fluconazole	TEA	Cure	NR
34/Ueng SWN	Fluconazole	TEA	Cure	NR
34/Ueng SWN	Fluconazole Amphotericin B ICS	TEA	Cure	NR
34/Ueng SWN	Fluconazole Amphotericin B ICS	TEA	Cure	NR
34/Ueng SWN	Fluconazole	RA	NR	NR
34/Ueng SWN	Fluconazole	RA	NR	NR
34/Ueng SWN	Fluconazole	RA	Dead	NR
42/Anagnostakos K	Caspofungin	TEA	Cure	28
42/Anagnostakos K	Fluconazole	TEA	Cure	22
42/Anagnostakos K	Fluconazole	TEA	Cure	70
42/Anagnostakos K	Fluconazole	TEA	Cure	15
42/Anagnostakos K	Fluconazole	TEA	Cure	36
42/Anagnostakos K	Fluconazole	TEA	Cure	47
47/Bartalesi F	Voriconazole Caspofungin + amphotericin B Amphotericin B	TEA	Cure 48
35/Wu MH	Fluconazole Amphotericin B ICS	RA	Cure	12
11/ Kelesidis T	Fluconazole	NR	Cure	12
12/Graw B	Fluconazole	TEA	Cure Dead (UD)	240
13/Bland CM	Liposomal amphotericin B + micafungin + fluconazole	RA	NR	NR
43/Dumaine V	Caspofungin + flucytosine Fluconazole + flucytosine	RA Arthrodesis	Cure	15
53/Lejko-Zupanc T	Liposomal amphotericin B + fluconazole Caspofungin	RA	Cure	36
54/Fabry K	Voriconazole (3 days) Oral voriconazole (7 months)	NR	Cure Dead (UD)	24
27 (/2004) Gaston G	Voriconazole Amphotericin B Amphotericin B ICS	RA	Amputation	6
48/Lazzarini L	Amphotericin B	RA	Cure	48
15/Wyman J	Fluconazole Amphotericin B	TEA	Cure	36
16/Phelan DM	Amphotericin B Ketoconazole Fluconazole	TEA	Cure	73
16/Phelan DM	NR	TEA	Cure	51
16/Phelan DM	Amphotericin B Fluconazole	TEA	Cure	70
16/Phelan DM	Fluconazole Fluconazole ICS	TEA	Cure	17
55/Açkgöz CZ	Fluconazole	RA	Cure	7.5

		Arthrodesis		
38/Bruce ASW	Fluconazole Fluconazole IB	TEA	Cure	84
38/Bruce ASW	Fluconazole Fluconazole IB	TEA	Cure Dead (UD)	48
56/Marra F	Fluconazole Amphotericin B ICS	RA (twice)	*E. coli* infection NR final outcome	NR
44/Merrer J	Fluconazole	NR	Cure Dead (UD)	11
36/Yang SH	Fluconazole	TEA	Cure	48
39/Ramamohan N	Amphotericin B + 5-flucytosine	TEA	Cure	24
57/Badrul B	Fluconazole	TEA	MRSA infection Cure	60
49/Wada M	Fluconazole	NR	Cure	36
17/Brooks DH	Amphotericin B Fluconazole	NR	Cure	24
40/Selmon GPF	Amphotericin B Itraconazole + fluconazole	OEA	Cure	48
18/Simonian PT	Ketoconazole	NR	Cure	72
50/Fukasawa N	Fluconazole	NR	*P. aeruginosa* infection Cure	24
19/Cushing RD	Fluconazole	NR	Cure	12
58/Nayeri F	5-flucytosine + amphotericin B 5-flucytosine + itraconazole	RA	Cure	22
20/Hennesy MJ	Amphotericin B 5-flucytosine	TEA	Cure	24
21/Cardinal E	Amphotericin B	RA	Cure Dead (UD)	NR
21/Cardinal E	Amphotericin B	RA	Cure Dead (UD)	12
21/Cardinal E	Fluconazole	RA	Cure	6
22/White A	Fluconazole Amnphotericin B Itraconazole	RA	Cure	24
23/Tunkel AR	Amphotericin B Ketoconazole Fluconazole	RA	Amputation	NR
41/Paul J	Amphotericin B + 5-fluorocytosine Ketoconazole	RA Arthrodesis	Cure	24
24/Evans RP	Amphotericin B	TEA	Cure	24
24/Evans RP	Amphotericin B	TEA	*S. aureus* infection Cure	60
25/Darouiche RO	Amphotericin B	RA	Cure	8
25/Darouiche RO	Amphotericin B	RA	Cure	1.5
25/Darouiche RO	Amphotericin B Ketoconazole	RA Arthrodesis	Cure	36
25/Darouiche RO	Amphotericin B	RA	Cure	5
26/Lambertus M	Amphotericin B	RA	*S. epidermidis* infection Cure	24
26 /Lambertus M	Amphotericin B Ketoconazole	RA Arthrodesis	Cure	14
27/Levine M	Amphotericin B	RA Arthrodesis	Cure	24
28/Iskander MK	Amphotericin B Ketoconazole	RA Arthrodesis	Cure	NR
29/Koch AE	Amphotericin B 5-flucytosine Ketoconazole	RA Arthrodesis	Cure	21
30/Lim EVA	Amphotericin B	RA	Cure	28
31/Younkin S	5-fluocytosine + amphotericin B	TEA	Cure	24
32/Lichtman EA	Amphotericin B Ketoconazole	RA	Cure	3
33/Goodman JS	Amphotericin B	RA	Cure	NR
33/Goodman JS	Amphotericin B	TEA RA Arthrodesis	Cure	12

10/MacGregor RR	Amphotericin B + 5-flucytosine	RA	Cure	12
45/Jenny JY	Caspofungine + 5-flucytosine Voriconazole + 5-flucytosine	OEA	Cure	24
45/Jenny JY	Voriconazole + 5-flucytosine Fluconazole + 5-flucytosine	OEA	Cure	36
9/Cobo F	Caspofungin Fluconazole	No surgical treatment	Cure	6
PR/Cobo F	Caspofungin 14 days Fluconazole (expected 6 months)	No surgical treatment	No relapse	3

UD: unrelated disease; **NR:** not reported; **PR:** present report; **TEA:** two-stage exchange arthroplasty; **RA:** Resection arthroplasty; **OEA:** one-stage exchange arthroplasty
ICS: impregnated cement spacer; **IB:** impregnated beads

Antifungal treatment

Seventy-five (98.6%) patients underwent antifungal treatment, with a single drug in 46 cases (60.5%), with two drugs in 16 cases (21%) and more than two in 13 (17.1%). Twenty-nine of the patients with monotherapy (63%) were treated with fluconazole and 14 (30.4%) with amphotericin B. One patient treated with amphotericin B alone suffered recurrence of the infection [33], while another patient treated with fluconazole alone died as a consequence of the infection [34].

Application of antifungal spacer cement was applied in ten (13.1%) patients (seven with amphotericin B and three with fluconazole).

Surgical treatment

Surgery was performed in 65 (85.5%) patients, 30 of whom (39.4%) underwent two-stage exchange arthroplasty; resection of arthroplasty without reimplantation was undertaken in other 30 (39.4%). One-stage exchange arthroplasty was undergone in 3 (3.9%) patients, and other procedures in two patients. Surgical treatment was not reported in 11 (14.4%) patients.

Outcome

The final outcome was not reported in four patients. A favourable outcome was found in 58 (76.3%) patients after antifungal plus surgical treatment, in 11 (14.4%) after antifungal treatment alone and in one after surgery alone. A patient experienced recurrence of infection with fluconazole therapy, but his outcome was positive with miconazole plus drainage of fluid abscess [46].

Regarding to the type of surgery, all patients who underwent a two-stage exchange arthroplasty cured, although two of them suffered a bacterial infection [24, 57]. From the patients treated with resection arthroplasty, one dead after fluconazole treatment [34], two suffered amputation [14, 23] and two were found to have a bacterial infection [26, 56]. All three patients treated with one-stage exchange arthroplasty cured [40, 45]. Our two patients are currently well with antifungal treatment only, and no relapse of disease has been observed in the short follow-up.

Discussion

PJI caused by *Candida* species is still a rare disease. However, the incidence is expected to rise because of the increasing number of patients implanted worldwide with joint arthroplasties [59, 60].

Risk factors for candidal infection, including immunosuppression, systemic disease and/or long-term antibiotics use, may play an essential role in the development of invasive candidal infections although other factors could be involved in triggering the infection, specially the presence of biofilm on bioprosthetic surfaces. Biofilm formation is considered the most prevalent growth form of microorganisms [61] and plays a key role in the development of clinical infections [62]. The majority of *C. albicans* infections are associated with biofilm formation on the host or on the surfaces of medical devices or prostheses [63]. Other factors, such as the adherence of *C. albicans* and their hydrolytic enzyme secretion may also have a strong influence on the development of PJI [64], and their modification may serve as possible targets for antifungal drugs against these infections.

Pain and swelling are the main symptoms of PJI due to *Candida* species, although the onset of symptoms can be insidious and development of the disease can be slow. Because symptoms are mild and there is frequently no diagnostic suspicion of PJI caused by *Candida*, the diagnosis can often be delayed. Another important problem is to elucidate whether the presence of *Candida* species in samples can be considered as a contaminant or not, because there is still no standard definition of PJI.

The treatment of choice for PJI caused by *Candida* species has not yet been established. The use of antifungal agents locally (mixed with cement) or systemically administered is a challenging issue. Locally, amphotericin B appears to be the ideal drug, but some studies have reported several problems [65, 66], while there is no report on the use of novel

antifungal drugs. However, this option has not been usually used, because from 76 cases reviewed, antifungal spacers were applied in only 10 (the majority of them with amphotericin B). In all cases the outcome was positive, but curiously in two patients with resection arthroplasty plus amphotericin B impregnated cement spacer application, an amputation [14] and a bacterial infection [56] was observed.

For systemic administration, lipid formulations of amphotericin B and fluconazole are the drugs of choice for this type of infection, and echinocandins may be an option [67].

Various authors have analysed the activity of some antifungal drugs against *Candida* biofilms. Two reports described resistance to fluconazole in these structures [68, 69], while another study found that it interfered with the development of *C. albicans* biofilms [70]. On the other hand, lipid formulations of amphotericin B have shown activity against *C. albicans* biofilms [70]. Anidulafungin was more active than amphotericin B against *C. albicans* biofilms of 24-h maturation, but amphotericin B was more active than anidulafungin against *C. albicans* biofilms of 48-h maturation [71].

In this review, various types of antifungal drugs have been used for treatment, and the majority of them with a positive result. In table 1, it can see that eleven patients (14.4%) were treated only with antifungal drugs [9, 11, 17-19, 44, 49, 50, 51, 54, and present report]; all these patients obtained a positive outcome, although the follow-up range from 3 to 72 months. According to these results, a correct and long treatment with antifungal drugs may be a good option, but due to the heterogeneity of the studies further research is required on this important issue, although it is highly recommended that these patients should be treated with drugs selected after antifungal susceptibility tests. In addition, a longer follow-up of these patients should be performed.

A two-stage arthroplasty exchange is currently considered the best approach in terms of eradication of the infection and preservation of the joint function in PJI caused by *Candida* species [4, 5]. Furthermore, when infection is chronic, this type of surgery is generally also recommended [72]. However, the success rate of this technique is controversial. One study reported a success rate of 93% for short-term infection control with 6 months of oral antifungal drugs after reimplantation [73], while another found that two-thirds of patients with PJ resection for fungal infection underwent reimplantation and that the infection was abolished in less than half of them [4].

On the other hand, resection arthroplasty was performed in around half of patients here reviewed (n=30). From these patients, in five of them the outcome was not initially favourable, and in three of them the final outcome was not reported. These results indicate that this procedure should not be the initial approach, also due to the important joint functional loss.

Regarding the third surgical method, some years ago Selmon et al reported a case with a positive outcome after a one-stage exchange arthroplasty [40]. Moreover, some authors have recently reported favourable outcome after one-stage exchange in selected cases of fungal PJI [45, 74]. In these cases, the responsible microorganism was identified post-operatively, with delayed specific antifungal treatment. In spite of this fact, the scientific evidence about these cases suggests that this technique may be appropriate in terms of eradication of infection, although the number of cases is still scarce. Further research should be done in order to establish the possible indications of one-stage exchange arthroplasty in cases of *Candida* PJI.

In summary, PJIs caused by *Candida* species are rare but fastidious infections that require a high index of suspicion because of their mild symptoms and insidious evolution. The diagnosis must be confirmed microbiologically and antifungal susceptibility testing of *Candida* strains is also highly recommended. The treatment is still not clearly defined and, although the association of long-term antifungal use with two-stage exchange arthroplasty is currently the gold standard to eradicate the infection, the analysis of the data of this review suggests the possibility of using one-stage exchange arthroplasty or antifungal treatment alone in order to obtain a favourable outcome for these patients. The next challenge for the scientific community is to establish the adequate algorithm for treatment in fungal PJI.

Informed consent

The patient described in this case report gave her informed consent for the inclusion in this publication.

Competing Interests

The authors have declared that no competing interest exists.

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