Contents lists available at ScienceDirect

Medical Mycology Case Reports

A case of *Candida orthopsilosis* associated septic arthritis in a patient with Systemic Lupus Erythematosus (SLE)

Orville D. Heslop [a,*], Karel De Ceulaer [b], Lois Rainford [a], Alison M. Nicholson [a]

[a] Depatrtment of Microbiology, University of the West Indies, Mona, Kingston7, Jamaica
[b] University Hospital of the West Indies, Mona, Kingston 7, Jamaica

A R T I C L E   I N F O

A B S T R A C T

We report a case of persistent *Candida orthopsilosis* associated septic arthritis. Repeated isolation of *C. orthopsilosis* from tissue and joint fluid was confirmed by identification of the ITS region of the rRNA gene using a *Candida*-Specific Luminex based assay and gene sequencing of the D1/D2 regions. This was the first case of *C. orthopsilosis* associated septic arthritis reported in Jamaica and in the literature.
© 2014 Published by Elsevier B.V. on behalf of International Society for Human and Animal Mycology. This is an open access article under the CC BY-NC-ND license (http://creativecommons.org/licenses/by-nc-nd/3.0/).

1. Introduction

The use of phenotypic methods has been limited in identifying closely related *Candida* species. Using genotypic methods, the clonally related species of *Candida orthopsilosis* complex was subsequently divided into groups 1, 2 and 3 identified under the corresponding names; *Candida parapsilosis*, *C. orthopsilosis* and *Candida metapsilosis* [1]. These were of sufficient differences to make them distinctly different species and should be viewed as separate clinical and epidemiological entities. These species have been implicated in several clinical conditions but with varying frequencies, including sex and age related differences [2].

C. parapsilosis is a major cause of disease in the immuno-compromised individual while *C. orthopsilosis* is comparatively rare in human infection despite its isolation from several clinical specimens [2–6].

Riccombeni et al. identified 5700 protein coding genes in *C. orthopsilosis*, the majority of which were similar to those found in *C. parapsilosis* [5]. These findings suggest that virulence of this species may be associated with expansion of gene families.

Up to 1992 only eight *C. parapsilosis* associated cases of septic arthritis were reported in the literature, seven of which followed replacement of a joint prosthesis, joint injection, or arthrocentesis [7]. To date, after an extensive literature search, no cases of septic arthritis caused by *C. orthopsilosis* have been reported.

We present a case of *C. orthopsilosis* infection associated with septic arthritis in a 28 year-old male presented at UHWI with a history of SLE. To the best of our knowledge this was the first case seen at the UHWI with no previously reported cases in Jamaica or in the literature.

2. Case

In March 2001 a 17-year-old Jamaican male diagnosed with Systemic Lupus Erythematosus (SLE) presented to the University Hospital of the West Indies (UHWI) rheumatology clinic with high fever, severe joint pains, proteinuria, and bilateral ankle edema. At that time, tests for both ANA and anti-DNA antibodies were positive, and a renal biopsy showed class I glomerulonephritis. He was treated with high dose steroids, which were quickly tapered because of steroid induced diabetes. His proteinuria decreased, but without clinical resolution. The patient was there-fore kept on Prednisone 20 mg daily with Mycophenolate Mofetil (MMF). The patient was readmitted in January 2002 and was regularly monitored with frequent blood cultures for sepsis, which yielded sterile cultures for microbiological investigations. The patient was however treated with augmentin following positive urine culture of *Escherichia coli*. His third admission in May 2002 was subsequent to a diagnosis of pylonephritis and skin sepsis.

Between January 2001 and May 2004 the patient had several clinic visits including sixth admissions to wards for fever and joint pains, pleurisy and renal flare. Pleural fluid and blood cultures were

Fig. 1. Radiograph of the left knee showing flattened condyles, presumably due to previous avascular necrosis. There is a marked periosteal reaction with mixed areas of lucency and sclerosis, suggestive of septic arthritis and osteomyelitis.

negative. In 2005 he developed bilateral avascular necrosis of the shoulders. He also experienced another renal flare with significant proteinuria (3.7 g per 24 h) but normal serum creatinine. From 2006 until 2009 he had frequent clinic visits and admissions because of fever, increased proteinuria and knee swelling.

Following recurrent painful swelling of the left knee in 2008, several aspirations of joint fluid were collected, yielding inflammatory fluid with negative bacterial cultures. Each aspiration was followed by a corticosteroid injection. Radiographs of the knees showed flattened condyles, presumably due to previous avascular necrosis (Fig. 1). Aspirations and steroid injections did not have any lasting effect as the left knee became increasingly painful several weeks after each aspiration. Despite negative cultures, antibiotics were prescribed but never produced any positive results. In August 2009 the renal status significantly deteriorated, necessitating one gram IV Methylprednisolone for 5 days. However, this treatment did not stabilize the renal inflammation and the patient was started on dialysis after another renal flare with acute renal failure.

Between March 2011 and February 2012, repeated cultures of tissue and joint fluids of the left knee on saboraud dextrose agar and mycobiotic agar, yielded yeast in pure cultures and were reported as *Candida sp* (not *Candida albicans*). These cultures, were subsequently identified by Remel and API 32 C as *C. parapsilosis* (Biomerieux API 32 C assimilation kit, reference code 6752175). Growth on cornmeal agar was characteristic of *C. parapsilosis* with yeast cells and philamentous hyphae.

In April 2012 empiric treatment was commenced with Fluconazole, and continued on a dosage of 200 mg twice per week, given after each dialysis.

Representative isolates of *C. parapsilosis* and subsequent isolate recovered from tissue and joint fluid in May 2012 were submitted to the Center of Disease Control and Prevention (Mycology Branch) for genotyping. These isolates were confirmed as *C. orthopsilosis*

using PCR primers D1: GCA TAT CAA TAA GCG GAG GA and D2: TTG GTC CGT GTT TCA AGA CG for amplification and sequence analysis of the ribosomal large subunit, D1/D2 and the internal spacer region of the rRNA as outlined by Deak et al. [8]. A *Candida*-specific Luminex-based assay using Probe CO (*C. orthopsilosis*) with a nucleotide sequence (5′ to 3′) of AA AAT TCT TCC AAA TTC GAC was used for rapid identification of the present isolate [8]. Primers used in the Luminex-based assay were ITS 3: GCA TCG ATG AAG AAC GCA GC and ITS4-BIOTIN: TC CTC CGC TTA TTG ATA TGC.

Among the many matches of *C. orthopsilosis* in Genbank we provide two strains including 100% match to Genbank # HM 755978.1 and HM 755977.1 (respectively equal to *C. orthopsilosis* strain ATCC 20504 and *C. orthopsilosis* strain ATTC 20503).

The minimal inhibitory concentration micro-dilution assay described by the National Committee for Clinical Laboratory Standards (NCCLS) [9] was performed on the *C. orthopsilosis* isolate and yielded susceptibilities to amphotericin B (AMB) ≤ 0.03 mg/L; fluconazole 0.25 mg/L; itraconazole ≤ 0.03 mg/L; posaconazole 0.06 mg/L; voriconazole ≤ 0.03 mg/L; flucytosine (5-FC) ≤ 0.125 mg/L; and ketoconazole 0.25 mg/L.

3. Discussion

C. orthopsilosis remains a rare entity in fungal associated human infections. Before 2005, *C. orthopsilosis* (group 2 strain) was yet to be differentiated from its closely related group 1, *C. parapsilosis*, and understandably so, as all previously associated infections were assigned to this species.

Several studies to adjust the number of infections previously attributed to *C. parapsilosis*, revealed estimated frequencies varying from 1.4% with *C. orthopsilosis* and 1.7% with *C. metapsilosis* in Spain to 10. 9% and 23.8% in South America and Malaysia [3–6,10]. To date however, there has been no reported case of *C. orthopsilosis* associated arthritis following an extensive literature search.

It is interesting to note that the present case is similar to previous cases where *C. parapsilosis* was implicated in arthritis in which there were persistent infections over several months despite antifungal treatment [7].

Consistent with these findings, is the prolonged period of treatment with fluconazole in the present case, but with no signs of improvement and the continued isolation of the yeast in pure culture. The prognosis therefore remains unclear, as the patient continues on fluconazole without any signs of resolution over the several months since antifungal therapy was first initiated.

Current reports on epidemiological studies have described *C. orthopsilosis* in only a few sporadic cases of clinical relevance [3–6,11]. However, its ability to infect and cause human diseases, appear to be similar to closely related *Candida spps. C. parapsilosis* for example, is closely related to *C. orthopsilosis* with many of their protein-coding genes having an ortholog in *C. parapsilosis* [5]. Of noteworthy interest, is a report on virulence by Gacser et al. [12]. They reported *C. orthopsilosis* as producing severe attenuation and morphological changes on reconstituted human tissue models [12].

Majority of the *C. parapsilosis* associated arthritis cases reported in the literature occurred with elderly patients (>60 years) following instrumentation of joints for placement of a joint prosthesis, joint injection, or arthrocentesis [7,13,14]. Comparatively, our patient is much younger (24 years at diagnosis) with a pre-compromised immune system apparently resulting from autoimmune disease SLE, and the frequent use of cortico-steroids introduced in patient therapy.

The persistence of infection seen in a number of *Candida* affected cases, appear to be more likely, the result of biofilm formation [15]. Biofilm formation confers significant resistance to antifungal therapy by limiting the penetration of antifungal drugs,

as well as, protect cells from host immune responses [15]. Some strains of *C. orthopsilosis* are able to form biofilms on silicone elastomer discs, which would increase the ability of the yeast to infect and cause disease [16]. Production of biofilms is a primary virulence factor of *C. parapsilosis* and apparently of greater significance than the small amount produce by *C. orthopsilosis* and *C. metapsilosis* [17].

Interestingly, the mortality rate of patients at an Italian University Hospital from whom were isolated *C. parapsilosis* which form biofilm in vitro, was 71.4% compared to 28% from those with biofilm-deficient isolates [11].

It is important to note that filamentous *C. parapsilosis* phenotypes generated more biofilm, and were more invasive into agar than strains, which remained predominantly in yeast forms [18]. The present *C. orthopsilosis* isolate is notably, a pseudohyphal yeast, observed on cornmeal agar.

The virulence of *C. orthopsilosis* and its capacity to produce disease has not been extensively studied. However, its closely genetically related *C. parapsilosis* [1] would reasonably suggest a strong possibility of similar invasiveness and clinical relevance of the two species. The prolonged treatment with fluconazole in the present case is similar to other cases of septic arthritis associated with *C. parapsilosis* [13].

Failure to carry out early investigations for fungal arthritis in our patient was probably due to the apparent lack of clinical suspicion. Presumably, as also seen in *C. parapsilosis* related cases, the source and dissemination of *C. orthopsilosis*, may have resulted from multiple injections of steroids in the joint including aspirations of joint fluid. The source of the organism may also have resulted from the contaminated hands of healthcare providers, which have been implicated in the transmission of *C. parapsilosis* [19]. A hematogenous spread of the yeast may have followed severe renal impairment, hemodialysis and avascular necrosis.

After 12 months of fluconazole therapy, *C. orthopsilosis* was isolated from joint fluid and tissue in pure cultures of the organism. MICs on repeated isolations of the fungus at different times, did not show any significant changes and remained at a low level of concentration for all the MICs done.

The repeated isolation of *C. orthopsilosis* in pure cultures followed by prolonged fluconazole therapy was consistent with the persistence of infection seen with other arthritic cases due to *C. parapsilosis* [19].

It is in our view, that the persistency of infection is a consequence of biofilm formation decreasing the concentration of fluconazole in the synovial fluid [15,17]. We believe that the resolution of this fungal infection will require the full course of continued treatment with fluconazole over a prolonged period of up to two years of antifungal therapy [15,17,20]. However, in the event of non-responsiveness to fluconazole, the echinochandins antifungals may prove useful, as they have shown high activity against biofilm forming *Candida* species [15,17]. Together with the appropriate management of the patient and the timely monitoring with cultures, may also play an important role in achieving complete clearance of the yeast.

Ethical statement

Written informed consent was obtained from the patient for publication of this Case report and any accompanying images. A copy of the written consent is available for review from the Series Editor of this journal.

Conflict of interest

There are none.

Acknowledgments

References

[1] Tavanti A, Davidson AD, Gow NA, Maiden MC, Odds FC. *Candida orthopsilosis* and *Candida metapsilosis* spp. nov. to replace *Candida parapsilosis* groups II and III. J Clin Microbiol 2005;43:284–92.

[2] Cantón E, Pemán J, Quindós G, Eraso E, Miranda-Zapico I, Álvarez M, et al. Prospective multicenter study of the epidemiology, molecular identification, and antifungal susceptibility of *Candida parapsilosis*, *Candida orthopsilosis*, and *Candida metapsilosis* isolated from patients with candidemia. Antimicrob Agents Chemother 2011;55:5590–6.

[3] Gomez-Lopez AA, Alastruey-Izquierdo A, Rodriguez D, Almirante B, Pahissa A, Rodriguez-Tudela JL, et al. Prevalence and susceptibility profile of *Candida metapsilosis* and *Candida orthopsilosis*: results from population-based surveillance of Candidemia in Spain. Antimicrob Agents Chemother 2008;52:1506–9.

[4] Lockhart SR, Messer SA, Pfaller MA, Diekema DJ. Geographic distribution and antifungal susceptibility of the newly described species *Candida orthopsilosis* and *Candida metapsilosis* in comparison to the closely related species *Candida parapsilosis*. J Clin Microbiol 2008;46:2659–64.

[5] Riccombeni A, Wolfe KH, Butler G. Sequence and analysis of the genome of the pathogenic yeast *Candida orthopsilosis*. PLoS One 2012;7:e35750.

[6] Tavanti A, Hensgens LAM, Ghelardi E, Campa M, Senesi S. Genotyping of *Candida orthopsilosis* clinical isolates by amplification fragment length polymorphism reveals genetic diversity among independent isolates and strain maintenance within patients. J Clin Microbiol 2007;45:1455–62.

[7] Weems Jr JJ. *Candida parapsilosis*: epidemiology, pathogenicity, clinical manifestations, and antimicrobial susceptibility. Clin Infect Dis 1992;14:756–66.

[8] Deak E, Etienne KA, Lockhart SR, Gade L, Chiller LT, Balajee SA. Utility of a Luminex-based assay for multiplexed, rapid species identification of *Candida* isolates from an ongoing candidemia surveillance. Can J Microbiol 2010;56:348–51.

[9] Wayne PA. Reference method for broth dilution antifungal susceptibility testing of yeast: approved standard M27-A. NCCLS. USA: National Committee for Clinical Laboratory Standards; 1997.

[10] Tay ST, Na SL, Chong J. Molecular differentiation and antifungal susceptibilities of *Candida parapsilosis* isolated from patients with bloodstream infections. J Med Microbiol 2009;58:185–91.

[11] Tumbarello M, Posteraro B, Trecarichi EM, Fiori B, Rossi M, Porta R, et al. Biofilm production by *Candida* species and inadequate antifungal therapy as predictors of mortality for patients with candidemia. J Clin Microbiol 2007;45:1843–50.

[12] Gacser A, Schafer W, Nosanchuk JS, Salomon S, Nosanchuk JD. Virulence of *Candida parapsilosis*, *Candida orthopsilosis* and *Candida metapsilosis* in reconstituted human tissue models. Fungal Genet Biol 2007;44:1336–41.

[13] Cushing RD, Fulgenzi WR. Synovial fluid levels of fluconazole in a patient with *Candida parapsilosis* prosthetic joint infection who had an excellent clinical response. J Arthroplasty 1997;12:950.

[14] Wada M, Baba H, Imura S. Prosthetic knee *Candida parapsilosis* infection. J Arthroplasty 1998;13:479–82.

[15] Iñigo M, Pemán J, Del Pozo JL. Antifungal activity against *Candida* biofilms. Int J Artif Organs 2012;35(10):780–91.

[16] Lattif AA, Mukherjee PK, Chandra J, Swindell K, Lockhart SR, Diekema DJ, et al. Characterization of biofilms formed by *Candida parapsilosis*, *C. metapsilosis* and *C. orthopsilosis*. Int J Med Microbiol 2010;300:265–70.

[17] Melo AS, Bizerra FC, Freymuller E, Arthington-Skaggs BA, Colombo AL. Biofilm production and evaluation of antifungal susceptibility amongst clinical *Candida* spp. isolates, including strains of the *Candida parapsilosis* complex. Med Mycol 2011;49:253–62.

[18] Laffey SF, Butler G. Phenotype switching affects biofilm formation by *Candida parapsilosis*. Microbiology 2005;151:1073–81.

[19] Trofa D, Gácser A, Nosanchuk JD. *Candida parapsilosis*, an emerging fungal pathogen. Clin Microbiol Rev 2008;21(4):606–25.

[20] Chan GF, Safwan M, Puad A, Aini N, Rashid A. *Candida orthopsilosis* and *Aureobasidium pullulans*: rare fungal pathogens causing persistent skin infection. Insight Infect Dis 2011;1:1–4.