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CASE REPORT

Superior vena cava *Candida krusei* septic thrombophlebitis in an ARDS patient on ECMO, with an unusual late complication

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SUMMARY

Candida-related bloodstream infections (BSIs) represent a severe condition associated with health care in the critical patient, with an increasing incidence of *Candida non-albicans* species. These infections could lead to several and unusual complications in high-risk patients due to various factors, including a prolonged hospital stay and invasive medical interventions. Here we report a case of a *Candida krusei* septic thrombophlebitis in an ARDS patient admitted to the ICU, complicated by a late onset prostatic abscess. To our knowledge, our patient represents the first reported case of a prostatic abscess due to *Candida krusei* treated with pharmacological therapy alone.

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INTRODUCTION

The Extended Prevalence of Infection in Intensive Care (EPIC-II) study has recently underlined the importance of Candida-related BSIs, demonstrating that 17% of acquired Intensive Care Unit (ICU) infections are caused by *Candida* species (Cornely *et al*., 2012). If we look at recent studies, they continue to report high mortality rates in up to 56% of those infections, despite the availability of efficient antifungal drugs (Pfaller *et al*., 2011a; Pfaller *et al*., 2011b; Benoit *et al*., 1998). The current use of antifungal prophylaxis and pre-emptive therapy in high-risk patients is aimed at reducing the prevalence of candidemia. Nevertheless, the benefits of these practices were extracted from cohorts of patients that were not considered in critical conditions (Collado *et al*., 2001; Haas *et al*., 1998; Yu *et al*., 1992). Furthermore, these strategies could risk the emergence of strains not susceptible to fluconazole, thus contributing to the increase in infections caused by *Candida non-albicans* (Caccese *et al*., 2012; Inai *et al*., 2014). As a result, the epidemiology of fungal infections could significantly vary among different geographical areas. The general incidence rate of candidemia caused by *Candida krusei* in Lombardy, Italy is 1% (Prigitano *et al*., 2020). In this regard, we report a case of a patient admitted to the ICU following a botulinum intoxication and later developing a BSI caused by *Candida krusei*.

Key words:
Candidemia, *Candida krusei*, Prostatic abscess, Septic thrombophlebitis, Echinocandin.

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CASE REPORT

A 58-year-old male without comorbidities was admitted to the intensive care unit (ICU) in Cagliari, Sardinia (Italy) in August 2013 due to an anaphylactic shock following a horse serum administration for a botulinum infection. His condition was later complicated by a septic shock caused by *Candida krusei*. He was then referred to our ICU at the Policlinico San Matteo Hospital in Pavia (Italy), where he was placed on ExtraCorporeal Life Support (ECLS) through veno-venous ExtraCorporeal Membrane Oxygenation (vv-ECMO) and Continuous Renal Replacement Therapy (CRRT). Furthermore, we started the patient on liposomal amphotericin B (AmB)

Table 1 - *AST report according to CLSI breakpoints of the C. krusei isolated on day 1 from blood culture withdrawn from the PV line.*

Antifungal drug	*MIC (mcg/ml)*
Anidulafungin	0,06 (S)
Micafungin	0,125 (S)
Caspofungin	0,25 (S)
Posaconazole	0,125
Voriconazole	0,12 (S)
Itraconazole	0,12 (S)
Fluconazole	256 (R)
Amphotericin B	0,5 (S)

MIC, minimal inhibitory concentration; S, susceptible; R, resistant.

empirically at our institute. Cultural exams performed on day 1 upon admission resulted positive for *C. krusei* in a urine sample (load: 10,000 CFU/ml) as well as in blood cultures collected from a subclavian central venous catheter (CVC) and a peripheral vein (PV) line. Consequently, the subclavian CVC was replaced, and cultural exams of its tip resulted positive for *C. krusei*. Fungal endocarditis was ruled out by performing a trans-oesophageal echocardiography (TEE) and a fundus oculi exam was negative for fluff balls. Upon receiving the Antimicrobial Susceptibility Testing (AST) report on *C. krusei* isolated from the blood culture sample (*Table 1*), the patient was started on an intravenous anidulafungin on day 4 and AmB was suspended as per ESCMID recommendations on the initial targeted treatment (Cornely *et al.*, 2012). Nevertheless, both blood (from a CVC) and urine cultures collected on days 20 and 23 respectively were still positive for *C. krusei* despite antifungal therapy and so AmB was added on day 23. As systemic arterial oxygenation and $PaCO_2$ started to improve, we gradually decreased the extracorporeal flow until vv-ECMO was successfully discontinued while maintaining protective mechanical ventilation. On the other hand, the patient's kidney function declined and inflammatory markers started to rise.

A computerized tomography (CT) scan was conducted and showed thrombophlebitis at the insertion site of the removed CVC. It involved the left internal jugular vein (LIJV), the left brachiocephalic vein and the superior vena cava (SVC) (*Figure 1*). The thrombus being a reservoir for *C. krusei* explained the blood cultures persistently resulting positive. The dual antifungal therapy with anidulafungin and AmB was continued, taking into consideration the molecular analysis of the FKS1 subunits and L701M mutation performed by our laboratory showing no apparent decreased echinocandin susceptibility in the *C. krusei* strain isolated from our patient's blood cultures on day 1 (Lallitto *et al.*, 2018).

Blood cultures drawn from CVC and PV lines on days 26, 32 and 37 were reported negative and we de-escalated antifungal therapy as per ESCMID guidelines (Cornely *et al.*, 2012). We initially suspended AmB on day 37, de-escalating from combination therapy to anidulafungin alone until we lastly suspended anidulafungin after 40 days of total antifungal therapy at our institute, guaranteeing at least 14 days of antifungal therapy from the first negative blood culture.

The value of inflammatory markers declined and respiratory and hemodynamic conditions improved in the following days, allowing for mechanical ventilation weaning on day 60. Systemic anticoagulation treatment with heparin was continued after discontinuing ECLS, and several CT scans were performed showing a progressive reduction of thrombophlebitis, with no apparent secondary foci of *C. krusei* infection. CRRT was discontinued upon renal function recovery, and the patient was discharged to a respiratory rehabilitation facility after 63 days of ICU stay.

On day 72, the patient went through another septic shock as a result of acute gangrenous cholecystitis requiring urgent cholecystectomy and another ICU admission at our ward. Urine culture exam on

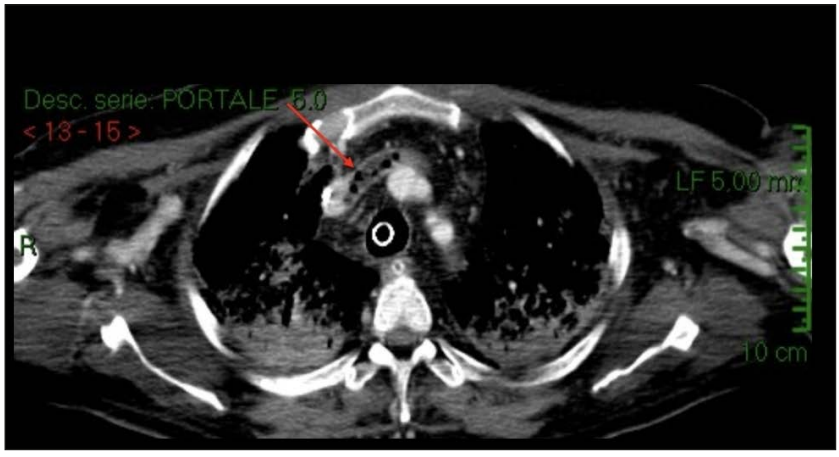

Figure 1 - *A CT scan showing a thrombophlebitis involving the left brachiocephalic vein and the superior vena cava (red arrow).*

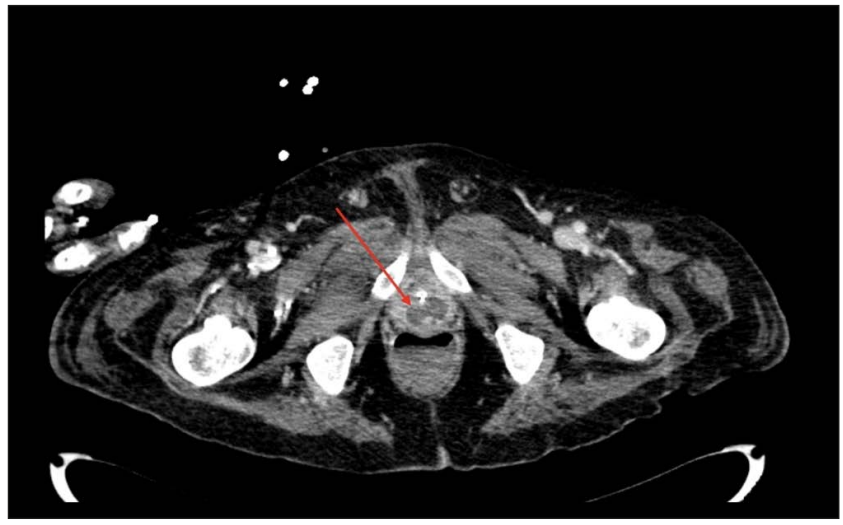

Figure 2 - *A contrast-enhanced CT scan showing a prostatic abscess (red arrow).*

readmission was positive for *C. krusei*, with blood cultures reported negative. A contrast-enhanced CT scan was performed, showing a prostatic abscess of a new onset (*Figure 2*). Prostatic secretion was then collected on day 94 for cultural exams, showing a high fungal load of *C. krusei*. We then reintroduced anidulafungin, which showed prompt radiological improvement of the prostatic abscess. As a result, conservative treatment was preferred and there was no need for surgical drainage.

The patient was finally discharged in good clinical conditions from our ICU to another rehabilitation facility after 142 days of hospitalization. He then returned to carry out his normal everyday activities 8 months after the initial event.

MICROBIOLOGY

The various blood cultures drawn from the patient were incubated in the BACTEC FX-BD culture system. Blood cultures drawn on day 1 from a CVC had a time to positivity (TTP) of 15 hours, while the peripheral line's TTP was 17.5 hours, indicating a catheter-related candidemia.

Once blood cultures were flagged positive, a Gram-stained slide was prepared directly from the positive blood culture bottles, revealing yeast-like structures under the light microscope. Additionally, a 10 µl aliquot was plated on nutritive and selective media following internal laboratory procedures. Biochemical identification of *C. krusei* was carried out on colonies grown on a Sabouraud Dextrose Agar plate using the API ID 32C test and was later confirmed using a Matrix Assisted Laser Desorption Ionization - Time of Flight (MALDI-TOF) mass spectrometry.

Sensititre Yeast One (TREK Diagnostic Systems, East Grinstead, West Sussex, UK) was used for the *in vitro* antifungal susceptibility test (AST) in broth microdilution (*Table 1*). We applied the Clinical and Laboratory Standards Institute (CLSI M27-A3, 2008) breakpoints in the AST report on *C. krusei* for echinocandins, amphotericin and azoles (Pfaller *et al.*, 2011a; Pfaller *et al.*, 2011b). Quality control strains (*Candida krusei* ATCC 6258, *Candida parapsilosis* ATCC 22019) were also included in the test, whose sensitivity results were within the ranges indicated by CLSI.

Mutations in the target regions (HS1 and HS2) of the FKS1 subunits and L701M are known to give rise to decreased echinocandin susceptibility in *C. krusei* (Prigitano *et al.*, 2014). Therefore, our mycology laboratory included the isolated *C. krusei* from our patient in a study analysing those regions in *C. krusei* isolates with low echinocandin MIC values (Lallitto *et al.*, 2018). The study concluded that none of the HS mutations were observed in any of the tested isolates; however, the L701M mutation was detected in 22/25 isolates, including our patient's. Nevertheless, the role of this change alone in causing reduced echinocandin susceptibility is still unclear.

DISCUSSION

The incidence of disseminated candidiasis has continued to increase over the last few years due to the widespread use of invasive medical treatments, namely intravascular devices, surgical procedures, prolonged broad-spectrum antibiotic therapy, and prolonged length of hospital stay.

Candida Thrombophlebitis of the Central Veins (CTCV) is a rare but insidious complication, having an impact on both the length and costs of hospital stay as well as morbidity and mortality in intensive care wards (Benoit *et al.*, 1998; Caccese *et al.*, 2012).

We analysed the last 30 years' literature and found 28 cases of CTCV, including the one described by our work (Caccese *et al.*, 2012; Inai *et al.*, 2014;

Hagiya *et al*., 2013); however, *C. krusei* was isolated in only one case (Pan *et al*., 2005). Management of these thrombophlebitis cases is controversial. Surgical removal, which is usually curative for peripheral thrombophlebitis, is not always technically feasible due to unreachable sites of infection. Prolonged medical therapy with antifungal drugs and systemic anticoagulation have shown good results, as observed in our case. Prompt replacement of the initial source of infection (i.e., the subclavian CVC in place at the time of admission to our ICU) as well as the removal of non-essential invasive devices is mandatory. Moreover, we cannot exclude the potential role of vv-ECMO cannulas and circuits in the maintenance of the infectious and systemic inflammation state. The dual therapy using lipophilic antifungals such as AmB and anidulafungin with good activity against biofilm allowed for good control of the infection and possibly prevented biofilm growth on cannulas and circuits, despite their low bioavailability in the urinary bladder and prostate (Zakhem *et al*., 2022).

The prostate is physiologically protected against infections thanks to the specific characteristics of its secretion, but prolonged urinary catheterization, urinary flux obstruction, haemodialytic treatments, neurological bladder, diabetes mellitus and wide-spectrum antibiotic therapy can foster prostatic abscess formation (Bastide *et al*., 2005; Ackerman *et al*., 2018; Ridgway *et al*., 2019). *Escherichia coli* is the primary pathogen demonstrating high pathogenicity in the prostate (Etienne *et al*., 2008), but recently the incidence of genitourinary fungal infections has been increasing sharply, mostly associated with the use of wide-spectrum antibiotics and immunosuppressive therapies (Ackerman *et al*., 2018).

To the best of our knowledge, this is the first *C. krusei* prostatic abscess to be resolved with pharmacological therapy alone. An accurate search in the literature demonstrated that only six case reports of fungal prostatic abscesses have been published since 1984, as shown in *table 2* (Bastide *et al*., 2005; Gupta *et al*., 2008; Collado *et al*., 2001; Haas *et al*., 1998; Yu *et al*., 1992; Lentino *et al*., 1984). Usually, these cases are mild and correlated to systemic infections, but they ought to be suspected whenever clinical improvement is not achieved after 48 hours of antimicrobial therapy (Ridgway *et al*., 2019).

Our patient persistently presented with urine cultures positive for *C. krusei*, but he developed clinical and radiographic signs of the prostatic abscess only after the second admission. The development of the prostatic fungal abscess was not associated with acquired or innate resistance to antifungal drugs, as demonstrated by our FKS1 region study. Instead, we suspect that the low bioavailability of echinocandins at that site, associated with prolonged urinary catheterization, played a significant role in its formation and persistence. Voriconazole usage associated with echinocandin has already been proposed for septic *C. krusei* thrombophlebitis, with good results (Pan *et al*., 2005). Nevertheless, we preferred anidulafungin to voriconazole, given its numerous drug-drug interactions, its possible renal toxicity when given intravenously, and the patient's recent abdominal surgery (Von Mach *et al*., 2006).

Table 2 - *A review of the literature showing six case reports describing fungal prostatic abscesses since 1984.*

Reference	*Patient*	*Therapy*	*Diagnosis*	*Pathogen*	*Recurrence*
Gupta *et al.*, 2008	72 years old	Micafungin, then transurethral unroofing	CT scan	*C. glabrata*	None
Bastide *et al.*, 2005	77 years old. HIV infection, type II DM	3-week course of fluconazole, then transrectal aspiration	Transrectal ultrasound	*C. tropicalis* in urine cultures and drainage fluid	After 7 days: TURP
Collado *et al.*, 2001	36 years old. Intravenous drug user, HIV and HCV coinfection	Ultrasound guided aspiration, then oral fluconazole	Ultrasound	*C. albicans* in drainage fluid	After 6 months: aspiration followed by 4 weeks of fluconazole
Bodner *et al.*, 1998	68 years old. Diabetic	TURP + two weeks of IV AmB	TRUS	*C. glabrata* in blood and urine cultures	None
Yu *et al.*, 1992	66 years old. Type 1 DM	Surgical drainage followed by 4 days of IV AmB, then fluconazole for 6 weeks.	–	*C. tropicalis* in urine and blood cultures, as well as pus drainage	None
Lentino *et al.*, 1984	72 years old. Type 1 DM	Surgical drainage without antimycotic therapy	–	*C. albicans* in pus	After 1 month: surgical drainage followed by a 6-week AmB course

CT; computed tomography, HIV; human immunodeficiency virus, DM; diabetes mellitus, TURP; transurethral resection of the prostate; HCV; hepatitis C virus, IV; intravenous, AmB; amphotericin B, TRUS; transrectal ultrasonography.

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