Diagnosis and management of a fatal case of sepsis caused by *Candida parapsilosis sensu stricto* in a neonate with omphalocele

Simone Santana[a], Tania Salci[b], Patricia Andriato[b], Patricia Bonfim-Mendonça[a], Silvana Caparroz-Assef[b], Melyssa Negri[a], Terezinha Svidzinski[a,*]

[a] *Medical Mycology Division, State University of Maringá, Av. Colombo, 5790, CEP 87020-900 Maringá, Paraná, Brazil*
[b] *Department of Pharmacology, State University of Maringá, Av. Colombo, 5790, CEP 87020-900 Maringá, Paraná, Brazil*

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ABSTRACT

We present a fatal case of persistent neonatal candidemia by *Candida parapsilosis* following omphalocele, without other anomalies. Despite an encouraging initial prognosis, after surgical correction and closure of the abdominal wall the case became difficult to treat, as in addition to the exposure of the patient to multiple risk factors for candidemia, antifungal therapy apparently was not adequate.

1. Introduction

Omphalocele is a congenital malformation in the abdominal wall, at the level of the umbilical ring, where there the closure of the abdominal muscles is incomplete. The child is born with herniation of the organs of this cavity, which are covered by a membrane composed of amnion and peritoneum. It affects 1 in 4000–10,000 live births and 1 in 3000–4000, including abortions and stillbirths [1,2].

Omphalocele is usually associated with other malformations, but the survival of patients with the isolated malformation is higher (92%) than in children with multiple (81%) or chromosomal abnormalities (24%) [3].

The treatment of omphalocele consists of the return of the herniated organs and the surgical repair of the abdominal wall. This surgery may be large-scale depending on the associated anomalies and the clinical conditions of the child [4]. In addition to surgical interventions, feeding difficulties, respiratory insufficiency and prolonged hospitalization are other predisposing factors to the infections frequently observed [5,6].

In recent years, *Candida parapsilosis* has emerged as one of the most common agents in candidemia in neonates in various parts of the world. However, as far as we know this species has not yet been described in cases of omphalocele. The present study reports the first fatal case of persistent neonatal candidemia by *C. parapsilosis* following omphalocele correction surgery, even under antifungal treatment.

2. Case

At 27 days old, a newborn was admitted (day 0) to the neonatal intensive care unit (ICU) of a university hospital in the south of Brazil, which is a reference center in neonatology. The birth, in another hospital, was *via* cesarean section at 39 weeks of gestation. The child was born with a weight of 2800 g, and presented omphalocele, evisceration of the bowel loops, which were reduced at origin, and complete closure of the abdominal wall within a few hours of birth. No other abnormalities were identified in the anatomical or laboratory tests of the child.

The history of the patient shows that the ceftriaxone antibiotic in a single dose and antibiotic therapy with oxacillin, amikacin and metronidazole were applied as post-surgical prophylaxis. Despite, the first blood culture, performed when the neonate was only 11 days old, were positive for *Staphylococcus aureus*.

In reference hospital the case followed its course, and the main events are summarized in Fig. 1. Clinical and laboratory finding like leukocytes and C-reactive protein (CRP) were used as indicators of patient follow-up.

On day 1 after admission to the reference hospital where this study was performed, the general condition of the patient worsened, requiring mechanical ventilation and the infusion of vasoactive drugs. Due to the isolation of yeast in the urine, empiric antifungal treatment with (1 mg/kg/day) amphotericin B deoxycholate (AMBd) for 28 days was initiated, and the antibiotic was changed to Tazocim. Surveillance blood cultures, from the peripheral vein were negative for bacteria of the KPC, VRE and MRSA groups, but confirmed fungal sepsis by *C. parapsilosis*.

On day 4 a relaparotomy was required, stenosis and intestinal malrotation were identified in this surgery. Despite the satisfactory healing of the surgical incision, the patient's condition worsened, and
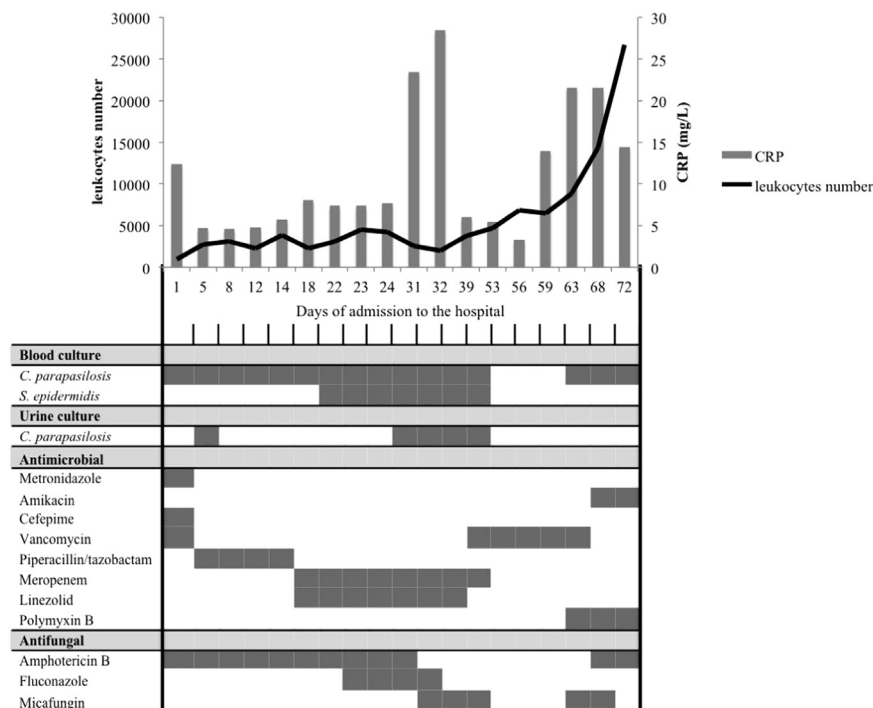
Fig. 1. Graphical representation of the main events that occurred during the evolution of the case over time. From day 1 sequential blood cultures were made and always the yeast isolated was identified as *Candida parapsilosis strictu sensu*. Prior to this period the patient had received the following antimicrobials: ceftriaxone (01 day); metronidazole (26 days); oxacillin (06 days); amikacin (05 days); cefepime (21 days); vancomycin (21 days); amphotericin B (28 and 8 days); fluconazole (12 days) and; micafungin (21 and 5 days), as well as laboratory tests; leukocytes and C-reactive protein (CRP) results.

was a further exchange of antibiotics (meropenem 30 days + linezolid). On day 13, considering the poor response to antifungal treatment, ophthalmological assessment, AIMG to investigate *Candida* endophthalmitis; and echocardiogram for to discard endocarditis, were performed. However, these tests were negative and on day 27 the same investigation was repeated, confirming the negative results and away the evidence these important indicators of severity in candidemia. Despite, there was worsening in the abdominal distension and respiratory discomfort, which justified a new laparotomy and ileostomy due to stenosis of the ileum.

On day 15, because of the persistence of sepsis the central venous catheter (CVC) was replaced, and culture of its tip was positive for *C. parapsilosis*. As well as blood cultures remained positive for *C. parapsilosis*.

On day 23, fluconazole was introduced, with (14 mg/kg/day) as dose of attack and (7 mg/kg/day) for maintenance. Later, on day 32 micafungin was added (14 mg/kg/day), by 21 days.

On day 53, the patient showed improvement, the blood culture was negative, for the first time, in addition leukocytes count and CRP serum level have decreased, so the antifungals were removed for observation.

On day 63, due a new blood culture positive for *C. parapsilosis*, micafungin treatment was returned (five days), with the patient presenting an improved general condition. On day 69, an oral diet was begun, which was accepted by patient, after that the child was discharged from the ICU to the pediatric ward. Despite the apparent improvement, both urine and blood cultures continued to show the persistence of *C. parapsilosis*.

On day 74, the patient displayed a worsening of the general condition, with no improvement of the infectious condition, despite the validity of amikacin, AMBd and polymyxin B. The infant then returned to the PICU in a severe condition, attributed to sepsis. After two days, on day 76, with 103 days of life, he died due to septic embolism.

2.1. Micological study

A total of 16 yeasts strains identified as *C. parapsilosis* (14 from the blood, 01 from the CVC and 01 from the urine) were evaluated (Table 1). All samples were previously identified by the classical method and confirmed by matrix-assisted laser-desorption/ionization time-of-flight mass spectroscopy (MALDI-TOF-MS). For this methodology the yeasts were prepared according to Spanu et al. [7] and the interpretation was performed in accordance with Pascon et al. [8], using a Microflex LT mass spectrometer (Bruker Daltonics) and FlexControl software (version 3.0, Bruker Daltonics). All isolates were confirmed as *C. parapsilosis sensu stricto*.

Genetic similarity was determined among the 16 clinical isolates of *C. parapsilosis* by Random amplified polymorphic DNA (RAPD), with two different primers: P4 (5′-AAGAGCCCGT-3′) and OPA-18 (5′-AGCT GACCGT-3′). For this assay, the samples were prepared according to Bonfim-Mendonça et al. [9]. The RAPD analysis identified the same band profile among *C. parapsilosis* samples, irrespective of the isolation site (Fig. 2) indicating that the same yeast isolate was found in all cultures.

The antifungal sensitivity tests for fluconazole, voriconazole, AMBd and micafungin were performed according to document M27-A3 of the Clinical and Laboratory Standards Institute (CLSI). All clinical isolates of *C. parapsilosis* were sensitive to the antifungals fluconazole, voriconazole and AMBd. Dose-dependent sensitivity and resistance was observed in all the clinical isolates for the antifungal micafungin results are presented on Table 2.

3. Discussion

We describe the case of a neonate with omphalocele but no other anomalies, who had apparently favorable clinical conditions, but who evolved to death due to complications of a fungal sepsis caused by *C. parapsilosis*. The omphalocele was isolated, in principle, with a positive prognosis [3], since the delivery was scheduled, with a full-term birth and a satisfactory weight that would apparently indicate favorable conditions for development, despite the omphalocele. However, from birth the child underwent several surgical interventions and was exposed to multiple risk factors: the prolonged use of multiple broad-spectrum antibiotics, CVC, NPT, mechanical ventilation for more than seven days; probes, prolonged hospitalization (103 days) at two hospitals, use of H2 blocker, bladder catheterization and gastrointestinal (GIT) surgery. In addition to the immunodeficiency related to the underlying disease, the patient was exposed to invasive procedures and the prolonged use of broad-spectrum antibiotics, which favor the

Table 1

Candida parapsilosis from different biological materials and antimicrobial therapy employed, related to the days of a neonate with omphalocele was admitted to the ICU of a University Hospital of southern Brazil.

	Days of admission to the hospital															
	1	5	10	15	19	27	33	35	38	48	53	57	69	74	75	76
Blood culture																
C. parapsilosis	X	X	X	X	X	X	X	X	X	X	X		X	X		
Urine culture																
Yeast	X															
C. parapsilosis						X	X	X	X	X	X					
CVC																
C. parapsilosis				X												
Antibiotic therapy	X	X	X	X	X	X	X	X		X	X	X	X	X	X	X
Antifungal therapy																
Amphotericin B	X	X	X	X	X	X	X						X	X	X	X
Fluconazole						X	X	X								
Micafungin						X	X	X	X				X			

X: Days in which isolation/treatment and invasive procedures occurred.

Antibiotic therapy: Metronidazole; amikacin; cefepime; vancomicin; piperacillin/tazobactam; meropenem; linezolid; polymyxin B.
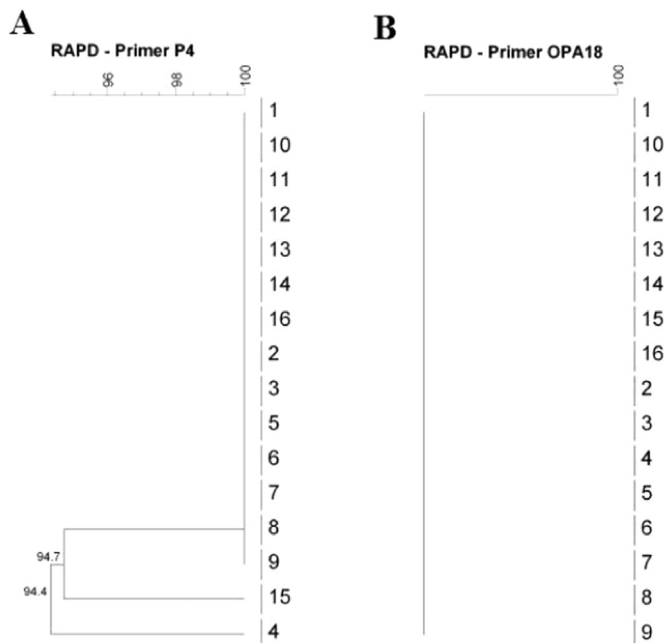
CVC: Central venous catheter.

Fig. 2. Genetic similarity among clinical isolates of *Candida parapsilosis* from different cultures from the patient case. RAPD methodology with initiators P4 (A) and OPA-18 (B). Molecular Weight pattern 100 pb (P) (Invitrogen). Lines 1, 2, 6–17: *C. parapsilosis* repeatedly isolated from blood cultures; 3 rows *C. parapsilosis* isolated from urine, line 5: *C. parapsilosis* isolated from catheter.

Table 2

Candida parapsilosis isolated from different clinical samples of a patient born with omphalocele hospitalized in the ICU of a University Hospital in the south of Brazil - sites and antifungal susceptibility profile *in vitro*.

N	Positive cultures (Days of life in which isolation occurred)	Days of admission to the hospital	Antifungals[*] MIC μg/ml (Cut-point)[**]			
			MCF	VRC	FLC	AMB
1	Blood (28)	1	4.00 (I)	0.03 (S)	0.25 (S)	0,5 (S)
2	Blood (32)	5	4.00 (I)	0.03 (S)	0.5 (S)	0,50 (S)
3	Blood (37)	10	4.00 (I)	0.03 (S)	0.5 (S)	0,50 (S)
4	Blood (42)	15	8.00 (R)	0.03 (S)	0.25 (S)	0,50 (S)
5	Blood (46)	19	4.00 (I)	0.03 (S)	0.25 (S)	0,25 (S)
6	Blood (54)	27	4.00 (I)	0.125 (S)	0.25 (S)	1,00 (S)
7	Blood (60)	33	4.00 (I)	0.125 (S)	0.25 (S)	0,50 (S)
8	Blood (62)	35	4.00 (I)	0.25 (I)	0.50 (S)	0,50 (S)
9	Blood (65)	38	8.00 (R)	0.125 (S)	0.50 (S)	0,25 (S)
10	Blood (75)	48	4.00 (I)	0.125 (S)	0.50 (S)	0,25 (S)
11	Blood (79)	52	4.00 (I)	0.125 (S)	0.25 (S)	0,5 0(S)
12	Blood (90)	63	4.00 (I)	0.125 (S)	0.25 (S)	0,50 (S)
13	Blood (96)	69	4.00 (I)	0.125 (S)	0.25 (S)	0,50 (S)
14	Blood (101)	74	4.00 (I)	0.06 (S)	0.50 (S)	0,25 (S)
15	Urine (54)	27	4.00 (I)	0.03 (S)	0.25 (S)	1,00 (S)
16	Catheter tip (42)	15	4.00 (I)	0.03 (S)	0.25 (S)	0,50 (S)
	MIC_{50}/MIC_{90}[***]		4.00/4.00	0.06/0.125	0.25/0.50	0.50/0.50

*MCF: micafungin; VRC: voriconazole; FLC: fluconazole; AMB: amphotericin B.

**MIC (Minimum inhibitory concentration): $\leq$ 2 μg/ml, (S); 4 μg/ml, (I); $\geq$ 8 μg/ml, (R).; VRC: $\leq$ 0.125 μg/ml, (S); 0.25–0.5 μg/ml, intermediate (I); $\geq$ 1 μg/ml, (R); FLC: $\leq$ 2 μg/ml, susceptible (S); = 4 μg/ml, susceptible dose dependent (SDD); $\geq$ 8 μg/ml, (R); AMB: $\geq$ 2 μg/ml, resistant (R).

***MIC_{50}: Minimum inhibitory concentration capable of inhibiting 50% of strains.

***MIC_{90}: Minimum inhibitory concentration capable of inhibiting 90% of strains.

increase the risk of fungal infection.

Surgeries in this site represent an additional risk factor for infections by opportunistic microorganisms, especially those that are part of the normal microbiota, such as yeast, and may facilitate the translocation of these microorganisms to the mesenteric capillaries, instituting hematogenesis infection [10].

The main pathogens involved in infections following GIT surgeries are components of the normal human microbiota, and prophylactic antimicrobial treatment is therefore, recommended, in order to reduce the microbial load at the surgical site [11]. The European Society of Clinical Microbiology and Infectious Diseases (ESCMID) guidelines recommends prophylaxis with fluconazole in these cases.

Although the patient was treated prophylactically with the ceftriaxone antibacterial, early cultures revealed *S. aureus*. Once bacterial infection was confirmed, metronidazole and cefepime were introduced.

Despite a good response to this type of infection, the prolonged use of antibiotics may favor fungal infection.

On day 15, the CVC was changed, due to the suspicion that it was colonized by *C. parapsilosis*, as has been recommended [12]. However, blood cultures remained positive for the same species, indicating the persistence of the infection and suggesting clinical resistance to the antifungal treatments used. The RAPD results confirm that the 16 isolates of *C. parapsilosis* identified in the blood, urine and catheter tip had the same band profile, indicating that besides common origin, several isolations of this yeast correspond to the same infectious process,

practically ruling out reinfections.

Advances in neonatal surgical techniques and perioperative care have contributed significantly to the results of omphalocele corrections. In the absence of other associated malformations, or chromosomal anomalies, death rates due to omphalocele are low, but the clinical course of this type of patient is still difficult to predict.

In this case, we highlight the difficulty in tackling antifungal therapy. AMBd was introduced immediately after the growth of *C. parapsilosis* in urine. This antifungal has been the recommended for the treatment of neonatal patients due to its fungicidal action and greater tolerance to adverse effects than adults have, and the prescribed dose was as usually recommended [12]. However, despite the *in vitro* low minimal inhibitory concentration (MIC) of AMBd against clinical isolates, the response was clinically unsatisfactory. In fact, despite the efficiency of AMBd *in vitro*, therapeutic failures have been reported [13]. It should be emphasized that there is a very limited number of antifungal agents available on the market that are capable of combating yeast infections. In addition, the indiscriminate use of this type of drug, associated with exposure to risk factors, has demonstrated a poor response to treatment [14].

In our opinion the introduction of fluconazole was late, and should have occurred at the beginning of the infection, since the pharmacokinetics of this antifungal guarantee high clearance in pediatric patients [15,16] justifying even the use of higher doses for their candidemia treatment [17]. However, the initial (14 mg/kg/day) and maintenance (7 mg/kg/day) fluconazole doses were lower than those proposed (25 mg/kg/day followed by 12 mg/kg/day) to rapidly ensure therapeutic levels [18].

In addition, micafungin, the most recent antifungal drug available in the health service, was the third antifungal introduced (Fig. 1) and, despite an apparent initial clinical improvement of the patient, it did not result in a favorable outcome, after this antifungal has been discontinued and returned. In fact, the *in vitro* MIC of micafungin was high, which confirms the inefficiency of the addition of this drug for the resolution of the infection. *C. parapsilosis* presents polymorphism in the *Fks1* gene, which makes this species naturally less susceptible to echinocandins, especially micafungin [18], and its introduction in this case would therefore not be scientifically support if there had been a protocol to be followed in the hospital.

Elevation of the CRP has been a useful marker for sepsis and has been clinically used to diagnose neonatal sepsis, as the of CRP serum level increases rapidly at the beginning of this infection. Serum CRP in this patient increased (13.8 mg/L) at the beginning of the infectious disease, coinciding with the first and peak (28.5 mg/L) detection of candiduria at 59 days of life with sepsis in course. However, the number of circulating neutrophils remained low (without neutropenia) most of the time (Fig. 1), increasing only in the last days of life.

In recent years, a growth of candidemia has been identified among the cases of neonatal infection [19] with a tendency towards increased *C. parapsilosis* [20]. This species is known by its ability to form a dense biofilm on medical devices such as CVC conferring its persistence and resistance to the antifungals. Moreover detached from biofilm yeast cells are important infections source. Recently it was showed that *C. parapsilosis* biofilm is associated with candidemia and it has an impact on mortality due to this infection [21]. Thus, it is possible to think, in the current case, *C. parapsilosis* firstly has formed a biofilm on CVC and next reached the blood flow being responsible by candidemia. Interestingly even changing the CVC, on day 15, the candidemia persisted.

The therapeutic approach to fungal infections remains a problem, as there is a lack of basic information and standardized protocols [22]. This fact is one of the predictors of the increase in mortality rates observed in candidemia, as cases such as this continue to occur. It should be noted that the patient died despite the low complexity of the condition and laboratory data indicating the agent, the sensitivity to antifungals and persistence of the same infection. Thus, the clinical management of surgical patients should be rethought, as fungal infection by *C. parapsilosis* is often neglected due to this yeast being originally part of the human skin microbiota.

Summarizing for this case it is important to highlight the possibility of candidemia in neonates with omphalocele. Furthermore it is necessary that the hospitals establish updated therapeutic approach protocols for candidemia associated with laboratory mycologic findings. Thus, clinical and laboratorial datas, properly interpreted, provide important information that contributes to the proper management of critical patients exposed to multiple risk factors.

Conflict of interest

The authors have no conflicts of interest to declare and confirm that each one has made substantial contributions to the information or materials submitted for publication.

Ethical form

The authors have obtained written and signed consent from the patient parents to publish the details of this case. This study has been approved by Ethics Committee with human people of Universidade Estadual de Maringá (UEM), under register number no. 615.643.

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