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Candida parapsilosis responsive to caspofungin in a preterm infant

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ABSTRACT:

The incidence of candidemia in the neonatal intensive care unit (NICU) is steadily increasing, with an estimated incidence of 1.6 to 9% in very-low-birth-weight infants and 15% in extremely-low-birth-weight infants. Here we report the case of a refractory candidemia by *Candida* parapsilosis successfully treated with caspofungin in a premature infant. The use of lysis centrifugation blood culture permitted to isolate *Candida* parapsilosis and the infant responded well to antifungal treatment, with a prompt improvement of his clinical condition. Caspofungin seems to be a valid option for infants with invasive candidiasis refractory to conventional antifungal therapy.

Key words: NICU, Candidiasis, *Candida* parapsilosis, Treatment failure, Caspofungin.

INTRODUCTION

The incidence of candidemia in the neonatal intensive care unit (NICU) is steadily increasing, with an estimated incidence of 1.6 to 9% in very-low-birth-weight infants and 15% in extremely-low-birth-weight infants[1,2]. Although *Candida albicans* is the organism most often associated with serious fungal infections, other *Candida spp.* have emerged as clinically important pathogens associated with opportunistic infections[3,4]. *Candida parapsilosis* is the second most common yeast species isolated from blood in Europe and South America and it is particularly associated with bloodstream infections in neonates and with catheter-associated candidemia[3,5].

Our report describes the case of a refractory candidemia by *Candida parapsilosis* in a premature infant, which was successfully treated with caspofungin.

CASE REPORT

In August 2010, a male infant weighing 2.6 kg was delivered at 35 weeks by cesarean section, after a twin pregnancy, and was admitted to our NICU for respiratory distress syndrome. His mother did not refer any disease during pregnancy and her laboratory exams were all normal.

After delivery, the infant needed surfactant therapy and nasal respiratory support. Some hours after delivery, the infant required intubation, a new dose of surfactant and endotracheal respiratory support for nearly one month [for ten days in High Frequency Oxygen Ventilation (HFOV)]. Chest X-ray at admission showed an image compatible with hyaline membrane disease grade IV. A Peripheral Inserted Central Catheter (PICC) was placed and empiric ampicillin plus gentamicin therapy as well as parenteral nutrition was started. Moreover, fluconazole prophylaxis at a dose of 6 mg/kg/die was begun. Echocardiogram showed a persistent ductus arterious Botalli, treated with ibuprofen for three days, and decreased myocardial kinesis, requiring dopamine and dobutamine. The child also underwent a Chest Computed Tomography Scan in order to exclude lung malformations.

Since the admission, surveillance cultures were performed. Twenty days after admission, the child showed

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an increased request of O_2, hyporeactivity, fever and signs of thrombocytopenia. Peripheral blood cultures (Isolator™ 1.5 microbial tubes - ISO 1.5 Wampole Laboratories, Princeton, NJ, USA) and mannan *Candida* antigen (Platelia® *Candida* antigen kits-Bio-Rad Laboratories) were performed. Blood culture was positive for *Candida parapsilosis* as well as the mannan antigen test. Liposomal amphotericin B (L-AmB, at a dose of 3 mg/kg/die) was started on day 20 and fluconazole was stopped. Stool culture and gastric aspirate were also positive. Disseminated candidiasis was evaluated by abdominal, renal and cerebral ultrasound scans, that were repeatedly normal. Ten days later, blood culture and the mannan antigen were still positive with appearance of thrombocytopenia, hyperthermia and hypertransaminasemia, as a consequence of L-AmB treatment. L-AmB was substituted with caspofungin, at a dose of 50 mg/m^2 for one day, then decreased at 35 mg/m^2.

Three days later the infant had a prompt clinical improvement, while thrombocytopenia and hypertransaminasemia resolved after 20 days. After 15 days of caspofungin therapy, the infant was extubated. Blood cultures and mannan antigen at day 10 and 18 of caspofungin treatment were negative. As a consequence, PICC was removed and caspofungin was discontinued, while the child was discharged with oral fluconazole for other 30 days (Table 1).

Pediatric neurologic evaluation was performed using the assessment of spontaneous motility according to Prechtl[6] at 1 and 3 months, with a normal result in both the assessments. A further neurological assessment was performed at 18 months using the Hammersmith Infant Neurological Examination[7], obtaining a score within the normal range.

DISCUSSION

In our report we describe the case of a premature infant with a bloodstream infection due to *Candida parapsilosis,* which was successfully treated with caspofungin.

Candida infections can be a life-threatening problem in long-term hospitalized adult and pediatric patients, especially in NICU[8]. Several investigators have described a predominance of *Candida albicans* and *Candida parapsilosis* as the etiologic species in neonates, accounting for 40 to 50% of neonatal candidemia each[9,10]. The identified risk factors for neonatal candidemia are low-birth weight, use of central venous catheters, parenteral nutrition, and broad-spectrum antibiotics[11-14]. Our patient had several risk factors for a *Candida* infection, such as preterm birth, endotracheal intubation, a history of exposure to antibiotics before the onset of candidemia (ampicillin, gentamicin and imipenem therapy), the presence of PICC (18 days before the onset of candidemia). Our patient had severe pneumonia possibly linked either to candidemia infection or to a chronic lung dysplasia without involvement of other solid organs. The gastrointestinal tract seems to be the site most frequently implicated in systemic dissemination[15], as a matter of fact both gastric aspirate and stool research for *Candida* were positive in our patient. Thus, it is important in *Candida* infections to verify a possible colonization of the gastrointestinal tract.

Conventional antifungal regimens, according to the Clinical Practice Guidelines for the Management of Candidiasis 2009[16], include amphotericin B and its lipid formulations and fluconazole as first step therapy. Although *in vitro* resistance to these drugs, especially for *Candida albicans* and *Candida parapsilosis*, is extremely low, recent studies and newer testing techniques report resistance rates of 2 to 7%[17]. In contrast, clinical treatment failure or persistence of the infection despite treatment with an appropriate dose is well recognized. Persistent infections could occur because an agent fails to reach an infected site in sufficient quantity, or because the patient's immune status is unable to eliminate the fungus even though its growth has been inhibited and, rarely, because of true drug resistance[18].

Current treatments for refractory invasive fungal infection remain inadequate even in adults, though newer

Table 1. Microbiological, treatment and laboratory parameters obtained at day 0, day 20, day 30, day 40, and day 58.

Variable	Day 0	Day 20	Day 30	Day 40	Day 58
Blood culture	Negative	C. parapsilosis	C. parapsilosis	Negative	Negative
Stool	Negative	C. parapsilosis	C. parapsilosis	Negative	-
Gastric aspirate	Negative	C. parapsilosis	C. parapsilosis	Negative	-
Mannan Antigen	<0.25 (negative)	0.58 (positive)	0.52 (positive)	<0.25 (negative)	<0.25 (negative)
White blood cell count (cells/µl)	25,840	31,580	21,220	12,210	9,200
Quantitative C Reactive Protein (mg/dl)	1.07	2.28	3.81	1.19	<0.10
Platelets (/µl)	205,000	16,000	12,000	130,000	544,000
Antimicrobial Treatment	Imipenem, Amikacin Gentamicin Fluconazole	Fluconazole Ambisome 3 mg/kg	Caspofungin 50 mg/m^2 35 mg/m^2	Caspofungin 35 mg/m^2 Removed	Stop therapy
Peripheral Central Catheter	Inserted			Removed	

drugs such as echinocandins have shown encouraging results. The clinical efficacy of caspofungin in neonatal candidemia have been described by several reports. Eun Sun Seo et al[19] described a case of *Candida albicans* candidemia in a VLBW infant, resistant to fluconazole and amphotericin B liposomial, successfully treated with caspofungin at high dose (4-6 mg/kg/day). They did not report any side effects for this protocol therapy. Nevertheless, one year before, Natale F et al[20] described a case of refractory *Candida krusei* candidemia in a VLBW preterm infant, resistant to other antifungal therapies, treated with caspofungin at standard dose, and they described acute liver failure due to the antimicrobial treatment. Elevation of liver enzymes and direct bilirubin values during caspofungin therapy have been previously reported in neonates[21]. In January 2009, Filippi et al. published two cases of neonatal liver abscesses due to *Candida albicans* infection effectively treated with caspofungin, the first one treated at a dose of 1 mg/kg daily, which is the lowest efficacious dose reported in literature[22], the second one with a dose of 5 mg/kg daily, without reporting any side effects. In the same year, Haase et al[23] described a case of *Candida albicans* septicemia in a preterm infant with congenital ichthyosis successfully treated with a combination therapy of L-AmB and caspofungin. In our report, we decided to introduce caspofungin as a salvage therapy, when clinical condition of the patient seriously deteriorated despite the usage of conventional antifungal drugs, which is similar to the findings of previous studies. Caspofungin treatment for 18 days did not show any increase of liver enzymes during the treatment and/or other side effects. We also think that the removing of PICC was helpful in the resolution of infection.

CONCLUSIONS

The caspofungin seems to be a valid option for patients with invasive candidiasis refractory to conventional antifungal therapy.

CONFLICT OF INTERESTS:

The Authors declare that they have no conflict of interests.

REFERENCES

1. Makhoul IR, Bental Y, Weisbrod M, Sujov P, Lusky A, Reichman B. *Candida* versus bacterial late-onset sepsis in very low birth weight infants in Israel: a national survey. J Hosp Infect 2007; 65: 237-243.
2. Gaynes RP, Edwards JR, Jarvis WR, Culver DH, Tolson JS, Martone WJ. Nosocomial infections among neonates in high-risk nurseries in the United States. Pediatrics 1996; 98**:** 357-361.
3. Pfaller, MA, Diekema DJ. Rare and emerging opportunistic fungal pathogens: concern for resistance beyond *Candida* albicans and Aspergillus fumigatus. J Clin Microbiol 2004; 42: 4419-4431.
4. Spellberg BJ, Filler SG, Edwards JE. Current treatment strategies for disseminated candidiasis. Clin Infect Dis 2006; 42: 244-251.
5. Sarvikivi E, Lyytikainen O, Soll DR, Pujol C, Pfaller MA, Richardson M, Koukila-Kähkölä P, Luukkainen P, Saxén H. Emergence of fluconazole resistance in a *Candida* parapsilosis strain that caused infections in a neonatal intensive care unit. J Clin Microbiol 2005; 43: 2729-2735.
6. Einspieler C, Prechtl HF, Ferrari F, Cioni G, Bos AF. The qualitative assessment of general movements in preterm, term and young infants—review of the methodology. Early Hum Dev 1997; 50: 47-60.
7. Haataja L, Mercuri E, Regev R, Cowan F, Rutherford M, Dubowitz V, Dubowitz L. Optimality score for the neurologic examination of the infant at 12 and 18 months of age. J Pediatr 1999; 135: 153-161.
8. Stamos JK, Rowley AH. Candidemia in a pediatric population. Clin Infect Dis 1995; 20: 571-575.
9. Avila-Aguero ML, Canas-Cota A, Ulloa-Gutierrez R, Caro MA, Alfaro B, Paris MM. Risk factors for *Candida* infections in a neonatal intensive care unit in Costa Rica. Int J Infect Dis 2005; 9: 90-95.
10. Makhoul IR, Kassis I, Smolkin T, Tamir A, Sujov P. Review of 49 neonates with acquired fungal sepsis: further characterization. Pediatrics 2001; 107: 61-66.
11. Komshian SV, Uwaydah AK, Sobel JD, Crane LR. Fungemia caused by *Candida* species and Torulopsis glabrata in the hospitalized patients: frequency, characteristics, and evaluation of factors influencing outcome. Rev Infect Dis 1989; 11: 379-390.
12. Bross J, Talbot GH, Maislin G, Hurwitz S, Storm BL. Risk factors for nosocomial candidemia: a case control study in adults without leukemia. Am J Med 1989; 87: 614-620.
13. Wey SB, Motomi M, Pfaller MA, Woolson RF, Wenzel RP. Hospital-acquired candidemia. The attributable mortality and excess length of stay. Arch Intern Med 1998; 148: 2642-2647.
14. Schaberg DR, Culver DH, Gaynes RP. Major trends in the microbial etiology of nosocomial infection. Am J Med 1991; 91(3B): 72S-75S.
15. Pappu-Katikaneni LD, Rao KP, Banister E. Gastrointestinal colonization with yeast species and *Candida* septicemia in very low birth weight infants. Mycoses 1990; 33: 20-23.
16. Pappas PG, Kauffman CA, Andes D, Benjamin DK Jr, Calandra TF, Edwards JE Jr, Filler SG, Fisher JF, Kullberg BJ, Ostrosky-Zeichner L, Reboli AC, Rex JH, Walsh TJ, Sobel JD; Infectious Diseases Society of America. Clinical practice guidelines for the management of candidiasis: 2009 update by the Infectious Diseases Society of America. Clin Infect Dis 2009; 48: 503-535.
17. Clancy CJ, Nguyen MH. Correlation between in vitro susceptibility determined by E test and response to therapy with amphotericin B: results from amulticenter prospective study of candidemia. Antimicrob Agents Chemother 1999; 43: 1289-1290.
18. Sanglard D, Odds FC. Resistance of *Candida* species to antifungal agents: molecular mechanisms and clinical consequences. Lancet Infect Dis 2002; 2: 73-85.
19. Eun Sun Seo, Geun Hwa Park, Sung Mi Kim, Hye An Jung, Byoung Kuk Kim. High-dose caspofungin salvage in a very-low-birth-weight infant with refractory candidemia. Korean Journal of Pediatrics 2010; 53: 2-239.
20. Natale F, Castronovo A, Regoli D, De Curtis M, Manzoni P. Successful treatment with caspofungin of refractory *Candida* krusei candidemia in a very low birth weight preterm infant. Pediatr Infect Dis J 2009; 28: 452.
21. Natarajan G, Lulic-Botica M, Rongkavilit C, Pappas A, Bedard M. Experience with caspofungin in the treatment of persistant fungemia in neonates. J Perinatol 2005; 25: 770-777.
22. Filippi L, Poggi C, Gozzini E, Meleleo R, Mirabile L, Fiorini P. Neonatal liver abscesses due to *Candida* infection effectively treated with caspofungin. Acta Paediatr 2009; 98: 906-909.
23. Haase R, Kreft B, Foell J, Kekulé AS, Merkel N. Successful treatment of *Candida* albicans septicemia in a preterm infant with severe congenital ichthyosis (Harlequin baby). Pediatr Dermatol 2009; 26: 575-578.