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A RARE CAUSE OF FUNGAL SEPSIS IN PRETERM NEONATE: A CASE REPORT AND LITERATURE REVIEW

REDAK UZROK GLJIVIČNE SEPSE KOD PRETERMINSKOG NOVOROĐENČETA: PRIKAZ SLUČAJA I PREGLED LITERATURE

Ilija Palić, Sonja Gojić
Intensive Care Unit, Institute of Neonatology, Belgrade, Serbia

ORCID iD: Ilija Palić https://orcid.org/0000-0002-9284-3173
Sonja Gojić N/A

Summary **Introduction**: Fungal sepsis is a serious bloodstream infection and an important cause of morbidity and mortality in preterm neonates. *Meyerozyma guilliermondii* (anamorph *Candida guilliermondii*) is an ascomycetes fungus, a saprophyte detected on human skin, gastrointestinal and genitourinary mucosa. This fungus is a rare cause of invasive infection, occurring in less than 5% of cases.
Case presentation: The preterm male neonate was delivered by emergency cesarean section at $28^{6/7}$ weeks of gestation with birth weight of 1590 g. On the 12^{th} days of life, the neonate developed signs of sepsis, associated with mild thrombocytopenia and increased concentration of C-reactive protein. *Meyerozyma guilliermondii* was proven in blood culture, while cerebrospinal fluid and urine were sterile. Respiratory and hemodynamic stability was maintained during infection. Fungal sepsis was treated with fluconazole, with a favorable outcome.
Conclusion: The importance of monitoring the clinical picture and laboratory parameters in neonates with fungal sepsis is emphasized when making a decision about the use of antifungal drug. In accordance with the current recommendations, the use of fluconazole prophylaxis reduces the risk of invasive fungal infection, especially in extremely preterm neonates with extremely low birth weight.

Keywords: preterm newborn, neonatal sepsis, *Candida*, invasive candidasis

Sažetak **Uvod**: Gljivična sepsa je ozbiljna infekcija krvi i značaj uzrok morbiditeta i mortaliteta kod preterminske novorođenčadi. *Meyerozyma guilliermondii* (anamorfa *Candida guilliermondii*) je gljivica iz grupe aktinomiceta, saprofit koji se nalazi na koži, gastrointestinalnoj i genitourinarnoj sluznici. Ova gljivica je redak uzrok invazivne infekcije, koja se viđa u manje od 5% slučajeva.
Prikaz slučaja: Muško preterminsko novorođenče rođeno je hitnim carskim rezom u $28^{6/7}$ nedelji gestacije sa telesnom masom na rođenju od 1590 g. U 12. danu života, novorođenče je razvilo znake sepse, udruženo sa blagom trombocitopenijom i povišenom koncentracijom C-reaktivnog proteina. *Meyerozyma guilliermondii* bila je dokazana u hemokulturi, dok su cerebrospinalna tečnosti i urin bili sterilni. Respiratorna i hemodinamska stabilnost bila je održana tokom infekcije. Gljivična sepsa je lečena flukonazolom, sa povoljnim ishodom.
Zaključak: Naglašen je značaj praćenja kliničke slike i laboratorijskih parametara kod novorođenčeta sa gljivičnom sepsom kada se donosi odluka o primeni antimikotika. U skladu sa trenutno važećim preporukama, primena flukonazola u profiktičkoj dozi smanjuje rizik od nastanka invazivne gljivične infekcije, naročito kod ekstremno nezrele novrođenčadi sa ekstremno malom telesnom masom na rođenju.

Ključne reči: preterminsko novorođenče, neonatalna sepsa, *Candida*, invazivna kandidijaza

INTRODUCTION

Fungal sepsis is a serious bloodstream infection and an important cause of morbidity and mortality in neonates born prematurely. The immaturity of the components of innate and acquired immunity, as well as long-term hospitalization of preterm neonates in neonatal intensive care unit (NICU) are the main risk factors for fungal sepsis (1,2). The most cases of neonatal fungal sepsis are caused by *Candida* species, i.e. *Candida albicans* and *Candida parapsilosis*. In recent years, the incidence of fungal infections in NICU caused by non-*albicans Candida* species has been increasing, especially in low- and middle-income countries. The overall incidence of invasive candidiasis in NICU ranges from 2% to 28% (2-5). The risk factors for neonatal invasive candidasis are presented in Table 1.

Meyerozyma guilliermondii (anamorph *Candida guilliermondii*) is an ascomycetes fungus, a saprophyte detected on human skin, gastrointestinal and genitourinary mucosa. This fungus is a rare cause of invasive infection, occurring in less than 5% of cases (6,7). Studies have shown an increased incidence of *Meyerozyma guilliermondii* infection in recent decades, along with a decrease in susceptibility to common antifungals, such as echinocandins and azoles (8). We presented a case of preterm neonate with fungal sepsis caused by *Meyerozyma guilliermondii*.

Korespondencija / Correspondence: Ilija Palić, Institute of Neonatology, Kralja Milutina 50, 11000 Belgrade, Serbia | E-mail: palicilija152@gmail.com
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Table 1 Risk factors for neonatal invasive candidasis
Tabela 1. Faktori rizika za neonatalnu invazivnu kandidijazu

- Prematurity
  prematuritet
- low birth weight
  mala telesna masa na rođenju
- low Apgar score
  nizak Apgar skor
- vaginal delivery
  vaginalni porođaj
- hospitalization in neonatal intensive care unit (> 7 days)
  hospitalizacija u jedinici neonatalne intenzivne nege (> 7 dana)
- endotracheal intubation
  endotrahealna intubacija
- mehanical ventilation
  mehanička ventilacija
- central venous catheters
  centralni venski kateteri
- use of broad-spectrum antibiotics
  primena antibiotika širokog spektra dejstva
- use of systemic corticosteroids
  primena sistemskih kortikosteroida
- total parenteral nutrition
  totalna parenteralna ishrana

CASE PRESENTATION

The preterm male neonate was delivered by emergency cesarean section at $28^{6/7}$ weeks of gestation with birth weight (BW) of 1590 g. The Apgar scores (AS) were 5 at first minute and 6 at five minutes after birth. A dichorionic diamniotic twin pregnancy was conceived through in-vitro fertilization and complicated by the pregnancy-induced hypertension and Hashimoto thyroiditis. Immediately after birth, the neonate was placed on non-invasive positive pressure ventilation (NIPPV) and surfactant was administered with INSURE methods. Also, the neonate received dual antibiotic therapy (ampicillin and amikacin), caffeine for stimulation of breathing and total parenteral nutrition.

The neonate was admitted to the NICU of our hospital on the second day of life (DOL), where noninvasive respiratory support and antibiotic therapy was continued. The cranial ultrasound (CUS) showed mild hyperechogenicity of the brain parenchyma in the periventricular region and grade II of intraventricular hemorrhage (IVH). Abdominal ultrasound and echocardiography showed normal findings.

On the 12th DOL, the neonate developed signs of systemic infection. Complete blood count (CBC) showed leukocytes of 13600/mm^3 (65% neutrophils and 25% lymphocytes), mild thrombocytopenia (119.000/mm^3), and increased concentration of C-reactive protein (CRP) of 20.3 mg/L. Cytologic and biochemical examination of cerebrospinal fluid (CSF) were normal. After the neonate's blood, CSF and urine sent for culture, dual broad-spectrum antibiotics with prophylactic doses of fluconazole was started. We received a positive result of the blood culture for *Meyerozyma guilliermondii*. Cerebrospinal fluid and urine culture were sterile. In accordance with the blood culture findings, the fluconazole at a therapeutic dose was continued.

Respiratory and hemodynamic stability was maintained during infection. A gradual decrease in CRP concentration and normalization of platelet counts is registered. Control CUS showed a gradual reduction of IVH. Antimycotic therapy (fluconazole) was administered for three weeks with favorable outcome.

DISCUSSION

Fungal sepsis is a potential life-threatening condition mostly seen in preterm and very low BW neonates (7,9). Flannery DD et al. (10) conducted prospective observational study about late-onset sepsis in neonates born before 29 weeks of gestation and reported that fungi were causative in about 5% of included neonates. However, a retrospective study that included neonates from 322 NICUs from 1997 to 2010 showed a decrease in the incidence of neonatal fungal sepsis. This was explained by the use of antifungal prophylaxis in very low BW neonates, as well as a decrease in the use of broad-spectrum antibiotics in NICUs (11). In perinatal history of our case, there were common known risk factors for fungal infections, such as prematurity, low BW, parenteral nutrition, previosly use of antibiotics and hospitalization in NICU more than 7 days.

Meyerozyma guilliermondii is an uncommon cause of late-onset fungal sepsis in neonates and seems to be one of the least virulent amongst *Candida* species. However, infections with this type of fungus are most commonly described among immunocompromised patients, often associated with hematological malignancies, gastrointestinal or cardiovascular surgery, and poor outcome (6,12,13). A literature search found several rare cases of fungal infections in neonates, most often born at term, caused by this type of fungus, often resistant to common antifungals drugs, such as fluconazole and amphotericin B. Raju U et al. (12) reported male full-term neonate with neonatal sepsis due to *Candida guilliermondii*, which manifested as meningitis and hyperpigmented macular lesions on the face, trunk, and extremities. This neonate treated successfully with fluconazole regardless of proven resistance to it. Similarly, Pasqualotto AC et al. (13) presented full-term female neonate with gastroschisis, treated with mechanical ventilation, broad-spectrum antibiotics and parenteral nutrition. This neonate had late-onset sepsis with proven *Candida guilliermondii* in blood culture and was successfully treated with amphotericin B. A case of a neonate born at term with a BW of 2.3 kg, with fungal infection caused by *Candida guilliermondii* and associated with necrotizing enterocolitis was recently reported (7). In contrast, our case is a male neonate born prematurely with low BW without other potential complications, such as meningitis, necrotizing enterocolitis, etc.

Treatment of fungal sepsis caused by *Meyerozyma guilliermondii* can be very challenging, given the frequent existence of resistance to conventional antifungals, such as fluconazole, amphotericin B, micafungin, etc (6,12). Also, significantly greater efficacy of voriconazole compared to fluconazole was demonstrated, regardless of geographical area. Special caution in the administration and dosage of these drugs is necessary in neonates, especially those born prematurely, due to immaturity of liver and kidney functions and changes in drug pharmacokinetics (4,14,15). However, despite frequent resistance, all reported cases of neonatal sepsis caused by this fungus had a favorable response to fluconazole or amphotericin B.

CONCLUSION

In conclusion, the importance of monitoring the clinical picture and laboratory parameters in neonates with fungal sepsis is emphasized when making a decision about the use of antifungal drug. The introduction of a second antifungal drug is not advised if the patient shows clinical and laboratory improvement after the use of previously initiated antifungal therapy. However, in accordance with the current recommendations, the use of fluconazole prophylaxis reduces the risk of invasive fungal infection, especially in preterm neonates born before 28 weeks of gestation with BW less than 1000 g.

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