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Candida Parapsilosis Neonatal Sepsis

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Abstract

Candida Parapsilosis (*C. parapsilosis*) infections are increasing in frequency worldwide with a significantly higher prevalence in neonates causing sepsis and invasive candidiasis, than in other at-risk populations. We report a case of late-onset neonatal sepsis in an eight-day-old low birthweight/preterm male neonate caused by *C. parapsilosis* with a fatal outcome.

Keywords: *Candida parapsilosis*, neonatal sepsis, low birthweight/preterm, amphotericin B

Introduction

Neonatal sepsis is an infectious clinical syndrome characterized by systemic inflammation and general damage of tissues. *Candida* species are the third leading cause of late-onset sepsis in premature infants and are associated with an increased risk of mortality and neurodevelopmental impairment among survivors (1). Colonization with *Candida* is common in premature infants and is an important risk factor for invasive disease (2). Historically, *C. albicans* is the most frequent cause of bloodstream infections, accounting for 70-80% of isolates (3). However, infections caused by *C. parapsilosis* are increasing in frequency worldwide with a significantly higher prevalence in neonates than in other at-risk populations (4, 5). In some centers, *C. parapsilosis* has emerged as the leading cause of invasive candidiasis (6). We report a case of late-onset neonatal sepsis in an eight-day-old low birthweight/preterm male neonate caused by *C. parapsilosis* with a fatal outcome.

Case Report

An eight-day-old low birthweight/preterm male neonate, a product of non-consanguineous marriage, delivered in a primary care facility at 35 weeks of gestation with birthweight of 1700 grams, was brought from a secondary to the tertiary care facility with history of abdominal distention and respiratory distress. He was discharged to home after birth on the 2nd day of life and readmitted on the 4th day with history of decreased feeding. He was kept in neonatal intensive care unit (NICU) of the secondary care facility on intravenous cefotaxime and amikacin. During the course of illness, he further developed abdominal distension with increasing gastric residues and respiratory distress.

On admission to the tertiary care facility, the baby had tachycardia and tachypnea with intercostal retraction, and mild abdominal distention. The baby's temperature was normal and he was euglycemic. Systemic examination revealed mild abdominal distention with no organomegaly, bilateral equal air entry, normal heart sounds, and well-flexed posture. Feeds were stopped and the baby was cared under radiant warmer with intravenous fluids, and vancomycin was added to the antimicrobial regime. On investigations, leucopenia, physiological hyperbilirubinemia, normal renal parameters and abnormal bowel gas pattern were observed. Arterial blood gas (ABG) was initially normal. Cerebrospinal fluid revealed meningitis. Aerobic, anaerobic and fungal blood cultures were requested. Initial urine sample sent for fungal hyphae was negative. Since there were indicators of sepsis in a preterm, a prophylactic antifungal fluconazole was also added to the regime.

During the NICU stay, the baby did not improve and continued to deteriorate clinically. Respiratory distress worsened and the baby was put on ventilator on the 3rd day of admission in view of abnormal ABG reports. Repeat urine exam revealed budding yeast cells. *C. parapsilosis* was isolated from blood as white colonies on Chromagar revealing budding yeast cells and susceptible to amphotericin B on the 6th day of admission. Despite addition of second antifungal, repeat ABG continued to deteriorate leading to demise.

Discussion

Preterm neonates have underdeveloped immune system leading to high susceptibility to environmental commensals in addition to known pathogens. This situation is further aggravated by indiscriminate use of antibacterials, leading to selective growth of fungal pathogens. *Candida* species are the third most common cause of bloodstream infection in premature infants. Candidiasis encompasses many clinical syndromes that may be caused by several species of *Candida*. The cumulative incidence is <0.3% among infants >2500 grams birthweight admitted to the NICU. The cumulative incidence increases to 12% for infants <750 grams

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birthweight. In addition, the incidence varies greatly by individual NICU. In the National Institutes of Health sponsored Neonatal Research Network, the cumulative incidence of candidiasis among infants <1000 grams birthweight is 2.4-20.4%. Up to 10% of full-term infants are colonized as the result of vertical transmission from the mother at birth, with slightly higher rates of colonization in preterm infants. Colonization rates increase to >50% among infants admitted to the NICU by one month of age. H_2 blockers and broad-spectrum antibiotics facilitate *Candida* colonization and overgrowth (7).

Invasive infections with *Candida* occur when the defense mechanisms of the host are compromised, allowing a colonizing strain to access the blood and deeper structures. Significant risk factors for neonatal invasive candidiasis include prematurity, low birthweight, exposure to broad-spectrum antibiotic administration, abdominal surgery, and presence of a central venous catheter. Unlike other fungal pathogens that are primarily acquired from the environment, systemic infection with *C. albicans* and *C. parapsilosis* occurs primarily with commensal organisms colonizing mucosal surfaces or skin (8). The shift from the commensal state to disseminated disease occurs in part due to alterations in host factors, alterations in competing microflora secondary to antibiotic use, or compromise in the integrity of mucosal surfaces. Unique properties of the commensal strain colonizing an individual patient also may play a role in the likelihood of dissemination and clinical outcomes. The immune system of premature infants has deficiencies in chemotaxis, cytokine production, phagocytosis, and production of type-specific antibodies. These immune defects combined with an underdeveloped layer of skin, need for invasive measures (endotracheal tubes, central venous catheters), and exposure to broad-spectrum antibacterials place preterm infants at great risk for invasive candidiasis (7). Preterm infants are also at high risk for spontaneous intestinal perforations and necrotizing enterocolitis. Both conditions require abdominal surgery, prolonged exposure to broad-spectrum antibiotics, and total parenteral administration requiring placement of central venous catheters. Each of these factors increases the risk of invasive candidiasis.

Candida exists in three morphologic forms: oval to round blastospores or yeast cells (3-6 mm in diameter); double-walled chlamydospores (7-17 mm in diameter), which are usually at the terminal end of a pseudohypha; and pseudomycelium, which is a mass of pseudohyphae and represents the tissue phase of *Candida*. Pseudohyphae are filamentous processes that elongate from the yeast cells without the cytoplasmic connection of a true hypha. *Candida* grows aerobically on routine laboratory media, but can require several days of incubation. *C. albicans* accounts for most human infections, but *C. parapsilosis*, *C. tropicalis*, *C. krusei*, *C. lusitaniae*, *C. glabrata*, and several other species are commonly isolated from hospitalized children.

A typical patient with invasive *C. parapsilosis* infection is a preterm very low birthweight infant with a central line receiving parenteral nutrition and on antimicrobials. Management includes removal of the central venous line and systemic amphotericin B therapy. Persistence of candidemia for five days or more is associated with an increased risk of ophthalmologic, renal or cardiac dissemination compared to infants with lower duration of candidemia (9).

Also, in any patients with an invasive fungal infection, additional foci of infection should be explored by cultures of urine and cerebrospinal fluid, echocardiogram, fundoscopy and sonograms of the kidneys and the liver. Liposomal amphotericin B may be an option in neonates with renal or hepatic dysfunction. Nearly a fourth of invasive *Candida* infections are associated with a concurrent bacterial infection, often coagulase negative Staphylococci and Enterococci that need appropriate antibacterial therapy (9). Empirical antifungal therapy has been advocated in neonates at a high risk of nosocomial infections such as those on cephalosporins or other clinical and laboratory parameters, but needs careful consideration (10).

Persistent *C. parapsilosis* fungemia on amphotricin B should lead to consideration of echinocandins as 'add on' or replacement therapy. Duration of antifungal therapy may vary from 2-3 weeks to 4 weeks in the presence of meningitis, 6-12 weeks for endophthalmitis and at least 6 weeks in endocarditis with or without surgical therapy.

The reported case initially had very nonspecific and slowly progressing findings of increasing gastric residues and abdominal distension with tachypnea. The baby had been on parenteral antibiotics for last five days without improvement of symptoms. These findings indicated towards a possibility of fungal sepsis as a cause of ill health. So on arrival, baby was started on fluconazole keeping this possibility. Blood cultures also corroborated *C. parapsilosis* as the cause, which was resistant to fluconazole. However the susceptibility pattern was not known initially and the second antifungal was added to regime late leading to unrelenting progress of the disease and fatality. This case again highlights the emergence of resistant *Candida* as a cause of late neonatal sepsis, especially with prematurity.

Prevention should target the horizontal transmission of *C. parapsilosis* in the neonatal unit. Monitoring and surveillance for *C. parapsilosis* infections, awareness and compliance with hand hygiene and bundled strategies for prevention infections, and antifungal prophylaxis are mandated (11). General preventive strategies include initiation of early human milk feeding to decrease dependence on central venous lines and parenteral nutrition. Judicious use of antimicrobials, avoiding broad-spectrum antibacterials such as cephalosporins, steroids, H_2 blockers and proton pump inhibitors is recommended. Antifungal prophylaxis strategies may be useful in decreasing colonization and subsequent invasive fungal infections.

Conclusion

A high index of clinical and microbiological suspicion is required for optimal diagnosis of *C. parapsilosis* infections in the premature neonate. *C. parapsilosis* infections are responsible for a third of neonatal *Candida* infections and have a mortality rate of approximately 10%. The reasons for predilection of *C. parapsilosis* infection in neonates are not clear but adherence to skin and biomaterials leading to biofilm formation may be important determinants. Amphotericin B is the antifungal drug of choice and combination therapy with caspofungin or other echinocandins may be considered in resistant cases.

Conflicts of Interest: None

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