Severe Modifications of Biological Markers in Late Neonatal Sepsis in a Very Low Birth Weight Due to Candida lusitaniae

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Neonatal sepsis is a major cause of neonatal mortality and morbidity in preterm, very low birth weight infants. Coagulase-negative staphylococcus and Candida spp. are among the most common causes of single infections and coinfections in neonates. Candida lusitaniae is rarely reported as an opportunistic pathogen in very low birth weight neonates. Early diagnosis and appropriate antifungal therapy can prevent morbidity and mortality in preterms especially in coinfections. Necrotizing enterocolitis is one of the most catastrophic gastrointestinal emergencies in premature infants in the intensive care neonatal unit, especially in preterm infants. Currently, the pathogenesis of necrotizing enterocolitis is believed to have multifactorial causes. We present the case of a very low birth weight preterm who developed necrotizing enterocolitis and sepsis caused by a coinfection of Coagulase-negative Staphylococcus and Candida lusitaniae.

Keywords: Candida lusitaniae, sepsis, very low birth weight preterm, coagulase-negative staphylococcus

Neonatal sepsis is a major cause of neonatal mortality and morbidity in preterm, (GA<37 weeks), very low birth weight infants (VLBW, BW ≤ 1500g). Coagulase-negative staphylococcus (CoNS) and Candida spp. are among the most common causes of single infections and coinfections in neonates. Candida lusitaniae is rarely reported as an opportunistic pathogen in very low birth weight neonates. Early diagnosis and appropriate antifungal therapy can prevent morbidity and mortality in preterms especially in coinfections. Necrotizing enterocolitis is one of the most catastrophic gastrointestinal emergencies in premature infants in the intensive care neonatal unit, especially in preterm infants. Currently, the pathogenesis of necrotizing enterocolitis is believed to have multifactorial causes. We present the case of a very low birth weight preterm who developed necrotizing enterocolitis and sepsis caused by a coinfection of Coagulase-negative Staphylococcus and Candida lusitaniae.

Experimental part

A 39-year-old patient, gravida 4, para 3, diagnosed with thrombophilia and preeclampsia was admitted in a level III maternity at 29 weeks and 6 days, 8 days prior to birth. She received treatment for pregnancy induced hypertension (PIH). The mean blood pressure remained high (170/110 mmHg) as it did not respond to treatment and cesarean section was performed at 31 weeks of gestation. She had negative peripheric and central cultures throughout the pregnancy, prior, during the hospitalization and after birth.

The male infant had a birth weight of 1450 g (P50%), a length of 45 cm (P75-90%), a head circumference of 30 cm (P25-50%) and a ponderal index of 1.59 (<P10%). Apgar scores were 7/8 at 1 and 5 min. Clinical examination in delivery room identified generalized cyanosis, diminished vesicular murmur, HR = 140 bpm and moderate tone.

The initial arterial blood gas showed metabolic acidosis and hypoglycemia which were corrected with intravenous (iv) bolus of normal saline and D10W solution. Blood cultures were sterile and the white blood count revealed 160/mm³, 31% neutrophils, 32% bands, 59% lymphocytes, 8% monocytes. The platelets count was 278000/mm³. He presented mild hypotension (blood pressure - BP = 50/21/30 mmHg) (fig. 1, table 1).

The infant was admitted in the NICU, placed at the thermal neutrality point in an incubator and received oxygen therapy as heated humidified high flow oxygen nasal canula, FiO2 of 0.25, parenteral nutrition (TPN), prophylactic antibiotic therapy (Penicillin and Colimycine). Due to mild hypotension and the metabolic acidosis (pH = 7.15, BE = -10.2 mmol/L, HCO₃⁻ = 19.3 mmol/L, lactate = 4.3 mmol/L) enteral feeding was not started.

We present a case of a preterm that developed late-onset sepsis after coinfection with CoNS and Candida lusitaniae.

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At 24 hours of life he presented abdominal distension and bilious gastric residue with streaks of blood of approximately 4 mL in the absence of feeding, present bowel sounds, and he eliminated meconium after enema. Blood tests showed hemoglobin = 18.5 g/dL, hematocrit = 60%, a white blood count of 9690/mm³, with 41% band neutrophils, 50% lymphocytes, 8% monocytes, with a platelet count of 229000/mm³, an oxygen saturation (SpO₂) > 94%, arterial partial pressure of oxygen (PaO₂) > 64 mmHg. No germs developed in the gastric lavage culture. He was kept nil per os (NPO) with TPN and Dopamine (3 mcg/kg/minute - mesenteric dose) and Tazobactam were added to the treatment.

On the 5th day of life blood tests showed, a white blood count of 8590/mm³, neutrophils, 31% bands, 59% lymphocytes and 9% monocytes, CRP = 0.5 mg/dL(<1mg/dL), PCT = 1.026 ng/mL (<0.5 ng/mL) and a stool culture was positive for CoNS (fig. 2). The abdominal X-ray revealed multiple dilated loops of gas filled bowel.

The stage diagnosis was necrotizing enterocolitis stage IA with CoNS. The pediatric surgery examination didn’t find anything surgically acute. The rectal exam showed a supple rectal ampoule with faeces with mucus. The barium X-ray for the upper gastrointestinal tract was normal, as well as the abdominal ultrasound. Necrotizing enterocolitis diagnosis has been confirmed.

On the 6th day a positive blood culture with *Candida lusitaniae* has been identified and the treatment was adjusted in accordance with Vancomycin and Fluconazole in therapeutic doses, NPO and TPN were maintained.

Similar laboratory results and positive stool culture for CoNS persists for another 8 days. Enteral feeding was initiated with delactosed formula for preterm infants (mothers’ milk was contraindicated because of PIH treatment) and stopped after 24 h due to gastric residue with digested milk in a higher quantity than administrated.

On the 14th day of life the infant still presented feeding intolerance. Laboratory tests revealed a sterile hemoculture and negative stool and gastric lavage cultures. The newborn was referred to pediatric surgery for reevaluation. Nothing surgically acute was found. On the 15th day of life after enteral feeding had started, he presented bilious vomiting with blood strips. On the 22nd day, in the absence of enteral feeding, CRP rises (9.2 mg %), PTC had a little higher than normal reference value (0.81 ng/mL), presepsin was normal (732 pg/mL), the stool culture was positive, again, for CoNS. The treatment with Vancomycin and Fluconazole continued.

Final diagnosis was late-onset sepsis with *Candida lusitaniae*, NEC with CoNS.

Enteral feeding was resumed on the 26th day of life, at the beginning with age appropriate formula and then with

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**Table 1**

NORMAL CBC VALUES ACCORDING TO BIRTHWEIGHT: 1200 - 1500G, [13]

| Day | Leucocytes/mm³ | Banded % | Lymphocytes % | Monocytes % |
|-----|---------------|----------|---------------|-------------|
| 1 - 3 | 10 800-14000 | 47       | 34            | 3           |
| 4 - 7 | 8 900-11 900 | 31       | 48            | 6           |
| 14 | 14 300 | 33       | 52            | 3           |
| 1 month | 11 000 | 26       | 59            | 4           |

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![Inflammation markers](image-url)

Fig. 2. The rise and fall of inflammation markers
mothers’ milk. The newborn was discharged at 51 days of life (38 postmenstrual weeks) at a weight of 2480 g (3rd percentile), breast milk feeding.

Results and discussions
Neonatal sepsis is a clinical syndrome manifested through systemic signs of infection and isolation of a bacterial pathogen from the bloodstream. Although a consensus definition for neonatal sepsis is lacking, it is classified according to the infant’s age at the onset of symptoms. Early-onset sepsis is defined as the onset of symptoms within the first 72 h of life and late-onset sepsis after 72 h of life for a preterm newborn [14].

The importance of Candida infections in the NICU has been recognized in the last few years, as it is the third most common cause of late onset sepsis in VLBW after CoNS and *Staphylococcus Aureus* [8].

CoNS and *Candida* are among the most common causes of single infections and coinfections in neonates after 72 h of age. The prevalence of neonatal sepsis is inversely correlated with gestational age and birth weight and therefore, in neonates, coinfection increases the rate of mortality threefold and results in significantly greater morbidity compared to those that result from single infections [1].

The positive cultures identified on the 5th and 6th day in the presented case suggest a nosocomial infection. The particular aspect is the bacteriological identification of CoNS and *Candida lusitaniae* in the same period of time, 5th and 6th day respectively.

VLBW neonates have a high risk for invasive fungal infections [15]. *Candida* spp. infections are responsible for 10-12% of nosocomial sepsis in VLBW infants, with a cumulative incidence of 1-4% among all NICU admissions [7]. Out of most newborns admitted to the NICU, 75% are colonized with *Candida* by the first month [16]. This yeast is an important pathogen in this immunocompromised group of patients, due to the associated high rates of mortality of up to 30% and morbidity, including significant adverse neurodevelopmental outcomes [4, 5, 16].

Compared to relative peers without invasive candidiasis these rates are 2 to 6 times higher in neonates with invasive candidiasis [5, 10].

The *Candida* species most commonly isolated from neonatal patients with invasive candidiasis is *Candida albicans*. However, recently there has been a significant rise in isolation rates for other species [17].

At first identified as *Candida parapsilosis* var. obtusa in 1954 [18], it was renamed *Candida lusitaniae* in 1959 [14]. Since it was first identified in 1979 in the context of an opportunistic infection in a patient with acute leukemia [20], *Candida lusitaniae* has been recovered from various sites in the human body including urine, bronchoalveolar lavage fluid, blood and peritoneal fluid, as well as from the kidney, vagina and the skin [21-25], mostly from immunocompromised patients including HIV/AIDS, cancer as well as neonatal or pediatric patients.

*Candida lusitaniae* is a pathogen more commonly associated to a group of immunocompromised patients, not normally present in the NICU, especially in the case of premature newborn infants, an aspect highlighted by the rarity of cases described in literature (table 2).

The development of the systemic candidiasis depends on the association between the hosts risk factors and the virulence of the candida species [33].

Usually affected newborns are admitted in the NICU and they require invasive therapies like central vascular catheters, endotracheal intubation and ventilation and are exposed to broad-spectrum antibiotherapy and parenteral nutrition [34].

It is also known that the transformation of *Candida lusitaniae* in a pathogen organism is favored by the presence of NEC, especially because preterms are compromised hosts for whom an opportunistic organism such as candida is a serious threat [35, 36].

**Table 2**

| Nr. | Ref. study | Study | Isolated Candida lusitaniae (no cases) | Age at birth | Median age at time of infection | Year | Evolution |
|-----|------------|-------|--------------------------------------|-------------|---------------------------------|------|-----------|
| 1   | [22]       | Sanchez PJ. *Pediatr Infect Dis J.* 1987; 6(5): 583-90. | 1          | 26 weeks | 7 days                          | 1987 | survived  |
| 2   | [14]       | Yaman AM. *Pediatr Infect Dis J.* 1992 Oct;11(10):878-80. | 1          | 26 weeks | 14 days                         | 1992 | survived  |
| 3   | [26]       | Oelzschal E. Am J Perinatol 1995; 10:313-5. | 1          | 30 weeks | 14 days                         | 1995 | survived  |
| 4   | [27]       | Fowler S. *Infection Control and Hospital Epidemiology. 1988;19(3):343-345. | 5          | NA      | 7 days apart                     | 1998 | survived  |
| 5   | [28]       | Vruses A. *European Journal of Clinical Microbiology and Infectious Diseases. 2002;21(4):204-209. | 1          | 3.5 weeks | 46 days                         | 2002 | survived  |
| 6   | [29]       | Pavek A. *Diagnostic Microbiology and Infectious Disease. 2003;47(1):331-339. | 1          | 30 weeks | 12 days                         | 2003 | Died      |
| 7   | [30]       | Fridkin SK. *Pediatrics. 2006;May;117(5):168C-1. | 46         | NA      | 20 days                         | 2006 | 3 died    |
| 8   | [31]       | Altaner E. *Microbiol Bul. 2010 Oct;44(4):593-603. Türkiz. | 1          | 35 weeks | 10 days                         | 2010 | NA        |
| 9   | [32]       | Cahan H. *International Journal of Pediatrics. 2011;2011:1-6. | 1          | 24 weeks | NA                              | 2011 | Died      |
| 10  | [41]       | Ozer C. *Clin Microbiol Infect. 2014 p2(09):926-41. | 1          | 25 weeks | NA                              | 2010 | NA        |
In the presented case the presence of CoNS in newborns stool cultures allowed the transformation of this species into a pathogen. Or perhaps the colonization of the newborn emerged as a sum of events including the cesarean section, the admission into NICU where he was subject to multiple manipulations. Important facts to consider in this case are the absence of umbilical or central catheters and lack of mechanical ventilation unlike the identified cases in literature [36–40].

Necrotizing enterocolitis (NEC) is one of the most catastrophic gastrointestinal emergencies in premature infants in the NICU, especially in preterm VLBW infants. Currently, the pathogenesis of NEC is believed to have multifactorial causes. Intestinal immaturity leads to a compromised intestinal epithelial barrier defense, altered vascular development and tonsus. Caesarean section, formula feeding, antibiotics, exposure to luminal microbiota together with compromised mucosal barrier can lead to inflammation and sepsis [11].

In the current case, a preterm of 31 weeks gestation, VLBW, could have the intestinal barrier affected during the perinatal period, considering the maternal pathology, in association with risk factors, caesarean section and formula feeding [40, 42].

According to the new NEC, the lining alteration is the result of the concomitant effect of the delay in nutrition initiation, the administration of antibiotics, the lack of use of mothers’ milk, after an initial possible intrauterine alteration due to changing of mesenteric blood flows secondary to maternal hypertension [42, 43].

Bowel damage is manifested as increased levels of lymphocytes from birth, values that persist if there is a clinical manifestation and positive culture for CoNS. On the other hand, an immature immune system partially able to identify pathogens is altered by the administered antibiotics. And so innate immune cells, lymphocytes, respond nonspecifically and do not provide long-term immunity [44].

The lymphomonocytosis present here from the first 24 hours, may be considered a first non-specific inflammatory answer by an immature immune system [45].

Furthermore, preterm infants who receive intravenous boluses, like in this case, associate greater risk to develop NEC [46].

Gastric residuals suggest feeding intolerance, however, it only indicates compromise of intestinal integrity when the residuals are either bloody or in excess with more than 30-50% of the previous feed [43, 47].

The NEC typical clinical pattern in the case of a preterm is determined by the terminal ileum localization manifested through abdominal distension, gastric residual and vomiting. In our case, the digestive tolerance was established after antifungal treatment was started. The treatment was effective so that digestive tolerance was evident and the administered treatment was resolved until after a 21 day antifungal and anti-staphylococcal treatment.

Conclusions

In the presented case the following scenario is possible. NEC with a known NICU pathogen for the last 30 years, CoNS respectively, favors the appearance of sepsis with a fungal pathogen in a patient with depressed immunity. The treatment was effective so that digestive tolerance was established after antifungal treatment was started. The mean weight gain after establishing digestive tolerance was 29 g / day.

Early enteral nutrition with breast milk appears to be the key to prevent these serious diseases for these utterly defenseless organisms as the preterms.

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