A preterm infant with intractable metabolic acidosis: a devastating presentation of *Chryseobacterium meningosepticum* meningitis

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Sepsis-related mortality and morbidity are the leading issues that neonatal intensive care units struggle with worldwide. We report a preterm infant with septic shock and intractable metabolic acidosis whose postmortem microbiologic examination revealed *Chryseobacterium meningosepticum* meningitis. We would like to alert clinicians about this uncommon sepsis agent, and to call into question the treatment modalities for metabolic acidosis.

***Key words:** Chryseobacterium meningosepticum, meningitis, metabolic acidosis, preterm.*

Chryseobacterium meningosepticum, a gram-negative bacillus that is widely distributed in nature but not normally present in the human microflora, is an important opportunistic pathogen of children[1]. Although this organism has been recovered from patients with community-acquired infections, it is most frequently an opportunistic nosocomial pathogen of infants 3 months of age or younger (75% of reported cases). The causes of nosocomial infections, including outbreaks, have been associated with contamination of solutions or equipment in the hospital environment (containers of antiseptic solutions, vials of intravenous drugs, aerosolized antibiotics, chlorinated water sources, respiratory care equipment) or sporadic infections due to indwelling devices, feeding tubes and other fluid-associated apparatuses[2,3]. Here, we would like to report a preterm infant with septic shock and intractable metabolic acidosis whose postmortem microbiologic examination revealed *Chryseobacterium meningosepticum* meningitis.

Case Report

A male infant was born to a 38-year-old mother by emergency cesarean section, conducted due to abnormal biometric and fetal doppler velocimetry tests at 27[3] weeks' gestation with a birth weight of 620 g. The mother suffered from HELLP syndrome and the detailed obstetric ultrasonography revealed intrauterine growth retardation (IUGR). Non-specific findings were determined in the histopathologic examination of the placenta. There was no consanguinity between the parents, and the infant's elder brother was healthy. The initial physical examination revealed respiratory distress. Surfactant replacement therapy was required and antibiotics (ampicillin, gentamicin) were initiated. The results of initial hematologic tests were as follows: hemoglobin, 15.7 g/dl; hematocrit, 40.0%; white blood cell count (WBC), 4.3×10^9/L; platelet count, 123×10^9/L; and absolute neutrophil count (ANC), 1.0×10^9/L. The first blood culture was negative. His blood gas parameters were pH: 7.29, pCO_2: 43.6 mmHg, pO_2: 67.6 mmHg, $cHCO_3$: 19.7 mmol/L, Lactate: 5.7 mmol/L. On the third day his general appearance and perfusion deteriorated. According to renewed septic screening, neutropenia (WBC: 1.8×10^9/L, ANC: 0.5×10^9/L) was detected, so granulocyte colony-stimulating factor (GCSF) was administered for two days. Also, blood gas analysis revealed a mixed acidosis (pH: 7.09, pCO_2: 66.5 mmHg, pO_2: 56.9 mmHg, $cHCO_3$: 16.1 mmol/L, Lactate: 2.0 mmol/L). Mechanical ventilator settings were revised, sodium bicarbonate support was initiated and

the antimicrobial spectrum was expanded with vancomycin, ceftazidime, amikacin, fluconazole and ornidazole. Afterward, the second blood culture was again negative. In addition, the metabolic tests (urine and blood amino acid paper chromotography, urine organic acid analysis and tandem MS analysis) for differential diagnosis of metabolic diseases were unremarkable.

In the following days, his neutropenia was recovered by GCSF, but thrombocytopenia persisted. His general state improved and sodium bicarbonate support was discontinued. On the tenth day, he became hyperglycemic and hypotensive; in addition, there had been bleeding from peripheral catheter entrances. Lumbar puncture (LP) could not be performed because of severe thrombocytopenia and cardiopulmonary instability. Based on the clinical and laboratory findings, he was considered to be in a state of septic shock, metabolic acidosis and disseminated intravascular coagulation. So the treatment was enriched with meropenem (meningitis dosage), intravenous immunoglobulin (IVIG), pentoxifylline, dopamine, sodium bicarbonate and fresh frozen plasma. On the eleventh day he developed pneumothorax and a chest tube was placed in his right pleural space. On the sixteenth day, massive hematuria developed and the metabolic component of the acidosis became more evident (pH: 6.95, pCO_2: 44 mmHg, pO_2:53 mmHg, $cHCO_3$: 11.3 mmol/L, Lactate: 11.7 mmol/L, Anion gap: 24). On the seventeenth day, because of intractable acidosis, peritoneal dialysis was initiated with a dialysate containing bicarbonate but no lactate. Under peritoneal dialysis his bicarbonate levels continued to drop while lactate and creatine levels rose. In addition, dichloroacetic acid was administered for lactic acidosis. His metabolic acidosis was so intractable that his pH could not even be raised above 7.00; $cHCO_3$ levels were below the detection limits. Finally, as a result of the deterioration in renal and cardiac function, he died on the 20th day of life due to sepsis-related intractable metabolic acidosis and multiple organ dysfunction syndrome. Although his postmortem blood culture was negative, culture of the cerebrospinal fluid (CSF) was positive for *C. meningosepticum*, which was highly resistant to aztreonam, ceftazidime, ciprofloxacin, imipenem/ meropenem, piperacillin/tazobactam, cefepime and cefoperazone/sulbactam, and sensitive only to sulfamethoxazole/trimethoprim and gentamicin. *C. meningosepticum* meningitis was the cause of this devastating clinical presentation.

Discussion

C. meningosepticum is a rarely detected gram-negative bacillus in clinical cultures. Infants become colonized with *C. meningosepticum* in the nose, throat or gastrointestinal tract before the development of invasive infection[4]. To date, the reported clinical presentations have been meningitis, sepsis, bacteremia, pneumonia, endocarditis, infections of the skin and soft tissue, wound infection, abdominal abscess, ocular infection, sinusitis, bronchitis, epididymitis, dialysis-associated peritonitis and prosthesis-associated septic arthritis[5]. Intractable metabolic and lactic acidosis related to *C. meningosepticum* meningitis has not previously been reported. Morbidity and mortality rates of neonatal meningitis due to *C. meningosepticum* are high; the mortality rate is more than 50%, and survivors frequently have severe neurologic sequelae, including hydrocephalus[5].

In addition to sporadic cases, many outbreaks of *C. meningosepticum* infection have been reported in the literature[2,6-8]. One of these reports was from our hospital, involving three clusters of eight newborns and five older children on five different wards, with seven different positive environmental cultures (health care worker's hand, infant formula, electrical buttons, computer keyboards, phone receivers, door knob and Ambu bags). Three of them had meningitis, two had primary bacteremia, five had sepsis, one had postoperative cellulitis and fasciitis, and two had respiratory distress and pneumonia. Seven of the 13 infants were preterm. Four infants (all of them were preterm) died (neonatal mortality rate was 50%); one preterm infant was discharged, with a sequela of hydrocephalus[6]. It is noteworthy that preterm infants in NICUs are at high risk for this invasive infection and the related mortality. Prematurity, IUGR and a history of HELLP syndrome in the mother were significant risk factors for the defective immune system in our patient. Also, colonization with the NICU flora, total parenteral nutrition, mechanical

ventilation, cytopenia and invasive procedures (placement of central venous catheters, chest tube, peritoneal dialysis catheter) probably resulted in a predisposition for nosocomial infections. The clinical state of the infant was such that LP could not be performed at that time. However, there is a report which notes that CSF evaluation can be unremarkable initially[9]. What would have changed could we have performed LP? It is difficult to say, because microbiological evaluation of the postmortem sample showed a highly resistant bacterium.

Optimal therapy for *C. meningosepticum* meningitis has not been well established. There are varying reports about the antibiotic susceptibility of *C. meningosepticum* isolates[9-11]. In one study, isolates remained susceptible to vancomycin, rifampicin and linezolid during the initial outbreak, while resistance to imipenem and amikacin increased in the second and third clusters[5]. Some authors noted that intravenous therapy with high-dose vancomycin and rifampin may be the optimal therapy for management of these infections[12]. However, in vitro susceptibility test results may not correlate with clinical efficacy in the case of this organism. Antibiotics with the most consistent in vitro activity against both *C. meningosepticum* and *C. indologenes* are minocycline, rifampin and levofloxacin[9,11]. In our case, the clinical response was poor under wide-spectrum antibiotics, and the postmortem culture antibiogram showed a highly resistant *C. meningosepticum* strain. According to the antibiogram, the strain we isolated was sensitive only to amikacin, gentamicin and trimethoprim-sulfamethoxazole. Although our patient was given gentamicin for 2 days and amikacin for 17 days, the clinical response was not successful, probably due to in vivo resistance. Rifampin should be kept in mind as a choice for treatment in a case of unresponsive sepsis.

In our patient, the most remarkable clinical sign was intractable metabolic acidosis. The gradual increase in the lactate levels and anion gap is thought to be secondary to sepsis and mitochondrial dysfunction. Lactic acidosis secondary to sepsis can be explained by impairment of oxygen delivery due to microcirculatory lesions and hypotension, impairment of oxygen utilization due to mitochondrial injury and decreased hepatic

clearance of lactate[3]. Previously, dichloroacetate treatment had been found successful in the treatment of refractory lactic acidemia of a preterm infant with group B Streptococcus sepsis and secondary metabolic acidosis[13]. Unfortunately, we did not secure a good response with dichloroacetate treatment. However, lactic acidosis and an increased glucose requirement due to sepsis have been reported in preterm infants. Significant elevations in plasma lactate levels were detected in septic infants while the pH was normal. Also, the glucose requirement increased significantly in the infected infants[14]. Hyperglycemia and hyperlactatemia in our patient were probably the results of the deterioration of glucose utilization and the balance of carbohydrate metabolism. It can be speculated that peritoneal dialysis exacerbated the clinical picture in our patient because of the deteriorated glucose metabolism and lactic acidosis.

By means of this instructive case, we would like to alert clinicians to this less common sepsis agent, which could lead to intractable metabolic acidosis, and to call into question the treatment modalities for metabolic acidosis in the case of impairment in glucose metabolism.

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