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Short communication

Pulmonary hemorrhage due to Coxsackievirus B infection—A call to raise suspicion of this important complication as an end-stage of enterovirus sepsis in preterm twin neonates

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ABSTRACT

Background: Prematurity is an important risk factor for the fulminate form of neonatal enteroviral infection. Pulmonary hemorrhage is a morbid complication that should be anticipated and managed aggressively due to its fatal outcome.
Objective: To emphasize the significance of pulmonary hemorrhage as a complication of severe enterovirus infection in preterm neonates.
Study design: This report is a description of the clinical history, medical management and clinical outcomes of two pairs of preterm twin newborns (30 weeks and 36 weeks) with fulminant infection due to Coxsackievirus B (CBV) infection.
Results: Maternal fever was reported in both deliveries and it was a factor in the decision for urgent cesarean section of the 30-week twins. Three of the four infants failed to survive. Their clinical course involved multiple organ system failure complicated with profound disseminated intravascular coagulopathy and pulmonary hemorrhage. Pulmonary bleeding leading to hypovolemic shock and respiratory failure was the direct cause of death in two cases.
Conclusions: This small series of preterm neonates with the diagnosis of CBV sepsis highlights the importance of correct diagnosis of maternal enterovirus infection in order to extend pregnancy and allow the fetus time to passively acquire protective antibodies. This report emphasizes the morbid complication of pulmonary hemorrhage as a result of enterovirus infection that should be anticipated and managed aggressively due to its potentially fatal outcome. Moreover, evaluation and observation of the asymptomatic twin is recommended in order to detect early signs of infection and deterioration in that sibling as well.

1. Background

Enteroviruses are positive-sense single-stranded RNA viruses associated with common causes of infection in infants and children [1]. Perinatal infection may be acquired in utero (via viremic maternal blood)[2,3], during labor from exposure to virus-positive cervical secretions [2,3], and after delivery from family members [4] or nursery outbreaks [5]. While most of the affected neonates have only mild illness, some are at especially high risk for developing life-threatening infections with poor prognosis. Pulmonary hemorrhage is a morbid complication for which there should be a high level of suspicion for the speedy implementation of aggressive management due to its fatal outcome.

Abbreviations: RDS, respiratory distress syndrome; DIC, disseminated intravascular coagulopathy; CSF, cerebrospinal fluid; PCR, polymerase chain reaction; IVIG, intravenous immunoglobulin; PICU, pediatric intensive care unit; GI, gastrointestinal; w, weeks of gestation; CNS, central nervous system.

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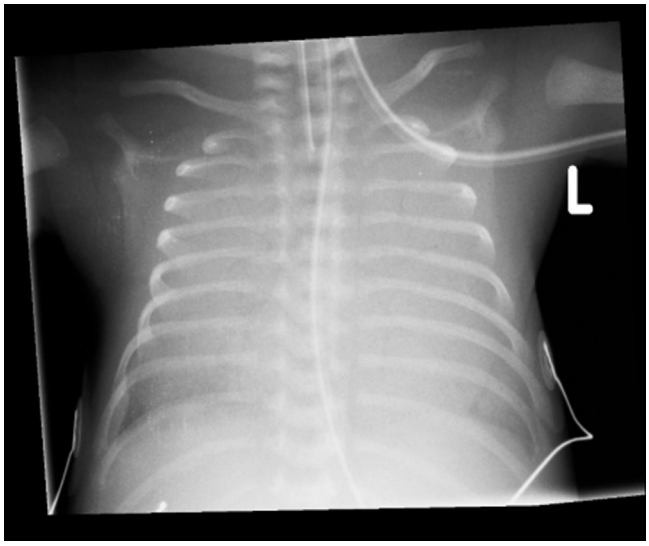

Fig. 1. Twin #1 of first set of twins. Chest X-ray demonstrating diffuse opacifications compatible with extensive pulmonary hemorrhage.

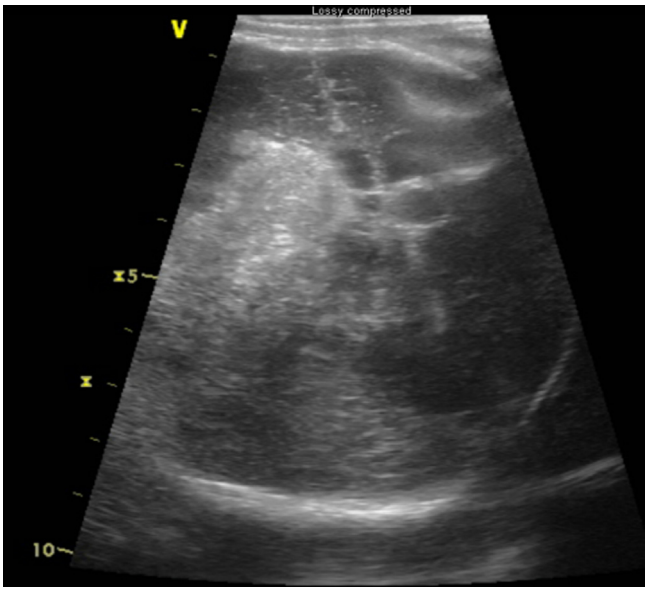

Fig. 2. Twin #2 of the first set of twins. Brain ultrasound demonstrating intraventricular hemorrhage grade 4 (right) and grade 3 (left) and deviation of the septum as a sign for the increased intracranial pressure.

2. Objectives

Between 2008 and 2014, two pairs of twin preterm newborns with enterovirus sepsis were hospitalized in our institution. They were all positive for Coxsackie B virus (CBV). Three of the four infants expired. We describe their clinical history, medical management and clinical outcomes.

3. Study design

3.1. The first set of twins (30 weeks)

These preterm twins were delivered by an urgent cesarean section after 30 weeks of gestation due to maternal severe abdominal pain, seizures and fever. Their initial clinical course was compatible with expected age-related prematurity problems. Both had rapid clinical deterioration and underwent a full sepsis workup on the 7th day of life. Real-time (RT) polymerase chain reaction (PCR) identified enterovirus in the cerebrospinal fluid (CSF) of twin #1 and in the stool of both twins and the mother. Sequencing was done by the Sanger sequencing technique [6] which identified it as CBV3.

3.1.1. Twin #1

On the 7th day of life had poor response, cutis marmorata and elongated capillary refill time. Laboratory abnormalities included new leukopenia, thrombocytopenia, abnormal coagulation studies compatible with disseminated intravascular coagulopathy (DIC), elevated transaminase, and combined respiratory and metabolic acidosis. His CSF was remarkable for mild pleocytosis with normal glucose and protein levels (Table 1). Antibiotic treatment was started promptly. During the next 24 h, he had overwhelming systemic sepsis, including hemodynamic and respiratory instability and refractory DIC. PCR for enterovirus in his CSF sample returned positive, and he received a single dose of intravenous immunoglobulin (IVIG, 1 g/kg). Acute respiratory failure due to massive pulmonary hemorrhage led to his death on the 8th day of life (Fig. 1).

3.1.2. Twin #2

Presented with cutis marmorata, tachycardia, elongated capillary refill time, hemodynamic and respiratory instability. His sepsis workup was remarkable only for consistent decrease in platelets count (Table 1). Antibiotic treatment was administered. Like his brother, he was leukopenic, with profound DIC that required large quantities of blood products. He received two doses of IVIG (1 g/kg). Ventilation was complicated with an episode of pulmonary bleeding. Hepatic dysfunction gradually developed and his neurologic status deteriorated. His repeated brain ultrasound on the 11th day of life revealed a new grade 4 intraventricular hemorrhage (Fig. 2). He died on the 12th day of life due to further neurological deterioration.

3.2. The second set of twins (36 weeks)

These preterm twins were born following a normal pregnancy and vaginal delivery at 36 weeks' gestation. The mother had a fever a few hours prior to delivery and the twins were treated with antibiotics until blood cultures returned sterile.

They were brought to the emergency room on their 5th day of life due to fever.

3.2.1. Twin #1

The physical exam and vital signs in the emergency room were normal and remarkable only for fever. He underwent a full sepsis workup: the CSF showed pleocytosis, mildly increased protein and decreased glucose level, and negative gram stain (Table 1). He was hospitalized and received antibiotics and antiviral treatment (acyclovir) for suspected herpes simplex virus (HSV) infection. The only remarkable laboratory abnormality during his first 2 days of hospitalization was new thrombocytopenia (Table 1). On his 3rd day of hospitalization, he suffered acute profound clinical deterioration, with paleness, cutis marmorata, low perfusion and undetectable blood pressure. He was transferred to the pediatric intensive care unit (PICU) and a massive pulmonary hemorrhage was diagnosed during intubation. He was stabilized for several hours, but then underwent acute deterioration secondary to additional massive pulmonary hemorrhage, resulting in hypovolemic shock that led to his death. His urine, CSF and blood cultures were sterile, RT-PCR from the CSF for HSV was negative, and RT-PCR from the CSF and from a rectal swab were negative for enterovirus. His post-mortem examination showed signs of inflammation in the brain,