Difficulty Breathing

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The following Brief Report was written by a resident. A discussion by a member of the resident's faculty follows. We invite any resident to submit such articles, together with commentary by a faculty member.

Patient Report

The patient was a 39-day-old white male who presented to a neighboring hospital with difficulty breathing, increasing irritability, and pallor. He was born at term via spontaneous vaginal delivery. The parents elected to have the delivery at home. The nurse midwife arrived approximately 10 minutes after delivery and the umbilical cord was clamped at that time. He did not receive prophylactic vitamin K and he was exclusively breastfed. In the referring hospital emergency center, a sepsis workup was done because of low-grade fever of 38°C and respiratory distress. The initial laboratory investigation showed anemia with a hemoglobin level of 8.6 g/dL, platelet count of 612,000/mm^3, and white blood cell (WBC) count of 21,200/mm^3. The spinal fluid showed WBC 3/mm^3, red blood cells 55/mm^3, glucose 95 mg/dL, and protein 39 mg/dL. A chest radiograph showed a widened mediastinum. Cefotaxime and ampicillin were administered after culture specimens were obtained and the patient was transferred to our pediatric intensive care unit. The infant was in considerable respiratory distress, very pale, and grunting. Capillary blood gas showed a pH 7.12, pCO_2 71 mmHg (9.5 kPa), pO_2 38 mmHg (5.1 kPa), which is consistent with acute respiratory acidosis caused by central airway obstruction. The patient was intubated and mechanically ventilated with normalization of blood gases. An echocardiogram demonstrated a structurally normal heart with a patent foramen ovale and a large anterior heterogeneous nonvascular mass in the location of the thymus, compressing the right ventricle and the main pulmonary artery. Coagulation studies were done because blood was oozing from the lumbar puncture (LP) site, peripheral puncture sites, as well as his gums. Prothrombin time (PT) was greater than 100 seconds, partial thomboplastin time (PTT) was greater than 100 seconds, fibrinogen 408 mg/dL, and D-dimer assay was less than 0.25 μg/mL.

Diagnosis: Late Onset Vitamin K Deficiency Bleeding

Hospital Course

A diagnosis of late-onset vitamin K deficiency bleeding (VKDB) was made and he was treated with 1 mg of intravenous vitamin K, and fresh-frozen plasma. The bleeding from the puncture sites stopped and the PT and PTT normalized to 9.7 and 27.9 seconds, respectively, 9 hours later. Chest computed tomography (CT) demonstrated a non-enhancing heterogeneous low-density mass in the anterior mediastinum consistent with acute thymic hemorrhage and compressing the airways (Figure 1). We decided to monitor the progression of the thymic mass by serial chest ultrasound (Figure 2). A repeat chest ultrasound 6 days later showed a decrease in the size of the mass with a liquefied central area giving further evidence

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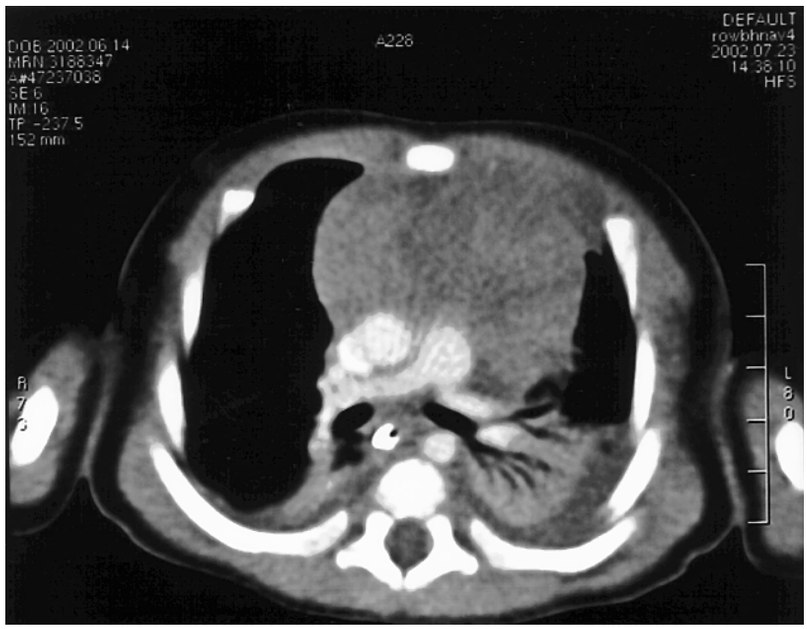

Figure 1. CT of the chest demonstrates a large non-enhancing, heterogeneous mass compressing the airway distal to the carina.

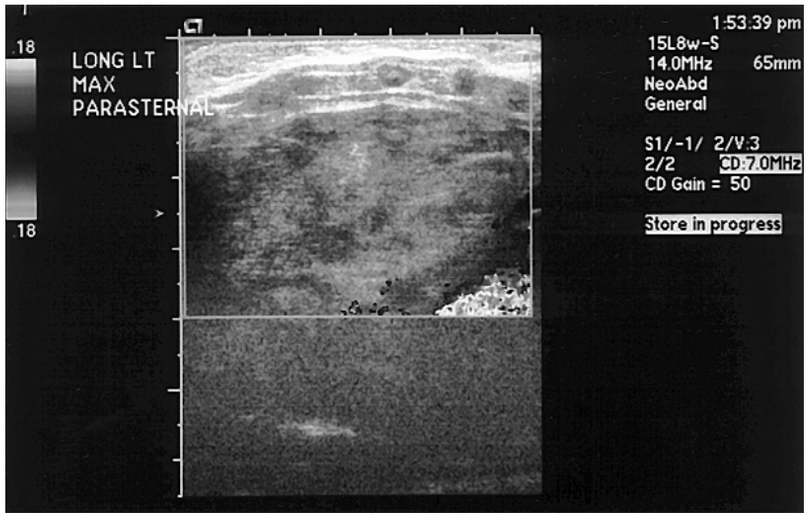

Figure 2. Ultrasound with Doppler flow of the chest reveals a 5.5 × 3.7 × 3.3 cm heterogeneous, non-vascular mass in the area of the thymus.

of an acute hemorrhage. CT of the head was normal without intracranial bleeding. Magnetic resonance imaging of the spine was normal and did not show an epidural hematoma at the site of the LP.

The respiratory failure improved and the endotracheal tube was removed 2 days after admission. The PT and PTT remained normal. He was discharged home after 5 days. Repeat chest ultrasound was normal after 1 month.

Commentary

Late-onset VKDB in infancy, formerly named hemorrhagic disease of the newborn, is caused by severe vitamin K deficiency between 2 weeks and 6 months of

age. It usually presents with intracranial hemorrhage. Neonatal prophylactic administration of intramuscular vitamin K prevents the development of late-onset VKDB except in severe malabsorptive disorders and cholestasis. Acute thymic hemorrhage is exceedingly rare, and to our knowledge, it has been described previously in only 2 infants with late-onset VKDB.[1,2]

Vitamin K deficiency bleeding in infancy is divided into early onset, classic, and late-onset VKDB. Early onset is very rare and is most often caused by maternal medications that interfere with vitamin K including warfarin, phenobarbital, phenytoin, rifampin, and isoniazid. Prophylactic vitamin K administration may not prevent early onset VKDB. Classic VKDB occurs between 2 and 7 days of age and is caused by a normally occurring decrease in vitamin K–dependent factors (II, VII, IX, and X) to as low as 30% by 48 to 72 hours of life. Poor placental transfer of vitamin K and the lack of bacterial flora in the neonatal intestines, which is responsible for the synthesis of vitamin K, are thought to cause this transient deficiency.[3] It is estimated that classic VKDB may develop in 0.25% to 1.7% of infants who did not receive vitamin K prophylaxis.[4] Prophylaxis with either IM or oral vitamin K, even with a dose as small as 25 μg, prevents classic VKDB.[3] Late-onset VKDB has a peak incidence between the 2nd week and 6th month of life. It occurs primarily in exclusively breast-fed infants who have received no or inadequate vitamin K prophylaxis, or in infants with cholestatic jaundice and intestinal malabsorption such as biliary atresia, alpha-1-antitrypsin deficiency, or cystic fibrosis.[4] Human breast milk contains 2.1 μg/L of vitamin K while commercial infant formulas have approximately 11.5 μg/L. Therefore a breast-fed infant consumes less than 1 (g of vitamin K per day. It is estimated that the incidence of late-onset VKDB, in the absence of vitamin K prophylaxis, is 40–100 per million live births.[5] Despite this apparent low incidence, late-onset VKDB has a poor prognosis because most of the infants present with intracranial hemorrhage leading to death or severe neurologic damage. Late-onset VKDB can be prevented with a single 1-mg IM vitamin K prophylaxis or repeated oral vitamin K prophylaxis at birth, 1 week, and 2–4 weeks, but not with a single oral dose of vitamin K after birth.[4,5]

Acute thymic hemorrhage is exceedingly rare in the neonate. A Medline search revealed 6 case reports.[1,2,6-9] Two of the cases presented immediately after delivery and were caused by early onset VKDB.[7,8] Both received IM vitamin K prophylaxis. Two other cases, as in ours, were caused by late-onset VKDB.[1,2] One received "the usual prophylactic dose of vitamin K1." He was a premature infant born at 36 weeks gestation and weight 2200 g at birth. Acute thymic hemorrhage typically presents with acute severe respiratory distress, anemia, and a widened mediastinum on chest radiography. The condition can be fatal.[7] Chest ultrasound is helpful in diagnosing and following the progression of the bleeding, it typically shows a nonvascular anterior mediastinal mass with a heterogeneous echostructure.[1,2] Mediastinal tumors are usually vascular on Doppler examination.

Infants born at US hospitals receive 1 mg IM vitamin K after birth. Parents who opt for "natural" delivery at home may decide not to give vitamin K and are likely to exclusively breastfeed their infants as part of the natural experience. This clearly increases the risk of classic and late-onset VKDB. There has been some controversies concerning vitamin K prophylaxis since the reports by Golding in the early 1990s.[10,11] Golding and colleagues reported an unexpected association between IM vitamin K prophylaxis and childhood cancer, especially leukemia. They did not find an association between oral vitamin K prophylaxis and childhood cancer and they recommended the use of oral vitamin K prophylaxis. Plasma concentrations of vitamin K after 1 mg IM injection are more than 10,000 times the endogenous level.[5] It was feared that such high vitamin K levels might explain that unexpected finding. Other population-based case-control studies suggested that the association between administration of IM vitamin K prophylaxis and leukemia was not likely.[12] Recent conclusions are that while small effects cannot be entirely ruled out, there is no convincing evidence that IM vitamin K increases the risk of childhood leukemia.[13] The American Academy of Pediatrics (AAP) issued a policy statement in 1993 questioning the data of Golding and suggesting that the apparent increase in acute leukemia was spurious.[4] The AAP stated that there was no evidence of an increase of childhood leukemia since 1947, well before IM vitamin K was first recommended for US children in 1961. The AAP recommended that vitamin K should be given to all newborn as a single IM dose of 0.5 to 1 mg.[4] We believe that the acute life-threatening thymic hemorrhage in our patient would have been prevented if he received the recommended IM vitamin K prophylaxis.

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