Thrombocytopenia and Anemia in Infants and Children

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ISOLATED THROMBOCYTOPENIA AND ANEMIA AS A PRESENTATION OF CHILDHOOD CANCER

Cancer, an uncontrolled proliferation of immature cells, can involve the bone marrow, with resultant abnormalities of peripheral blood cell counts. In leukemia, the most common of the pediatric cancers, the presenting signs and symptoms are a reflection of these events. The most common presenting symptoms are fever, pallor, purpura, and pain. The most common physical examination findings include hepatomegaly, splenomegaly, diffuse lymphadenopathy, and central nervous system (CNS) symptoms. Other common laboratory abnormalities include an increased or decreased total white blood cell count, circulating blasts, elevated lactate dehydrogenase, and elevated uric acid. The onset may be abrupt or chronic. The evolution of symptoms may proceed over a few days, weeks, or months. At first, symptoms may be nonspecific and may mimic other nonmalignant conditions. Fever, particularly if coupled with other nonspecific complaints, may mimic more common pediatric illnesses. Over 70% of children with acute lymphoblastic leukemia (ALL) will present with a platelet count of less than 100,000/μL, of which 20% have less than 20,000/μL.[1] Isolated thrombocytopenia has been reported to be extremely rare in childhood presentation of ALL. A review of the records of 2239 children enrolled in Pediatric Oncology Group or Children's Cancer Group trials in the 1980s showed that none of these children had significant thrombocytopenia with any other hematologic or physical manifestations of ALL when they were first seen by a hematologist.[2] However, because children previously treated with steroids were excluded from participation in these studies; those children presenting with isolated thrombocytopenia and treated inappropriately for immune thrombocytopenic purpura (ITP) would not have been captured in this data. Similarly, anemia occurs in over 75% of patients ultimately diagnosed with leukemia. The anemia is usually gradual in onset, normocytic, and rarely associated with significant

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symptoms. However, isolated anemia, in the absence of other signs or symptoms, is an extremely rare presentation. When confronted with a child or adolescent patient presenting with isolated thrombocytopenia or anemia, the concern for cancer should be minimal if there are no other common signs or symptoms.

THROMBOCYTOPENIA

Neonatal Thrombocytopenia

During fetal life, the platelet count progressively increases and reaches a level of approximately 150,000/μL by the end of the first trimester. Healthy fetuses and neonates at gestational ages of more than 22 weeks have a platelet count within the normal range for adults (150,000–450,000/μL). Thrombocytopenia is a rare occurrence in the general newborn population. When studied prospectively, a platelet count of less than 150,000/μL was found in less than 1% of newborns.[3] However, the incidence among neonates admitted to the neonatal intensive care unit is as high as 35%.[4] The rate of thrombocytopenia in the neonate increases as the gestational age decreases.[5]

In neonates, the underlying cause of thrombocytopenia can often be predicted by the timing of the onset of thrombocytopenia. The natural history of thrombocytopenia is also predictive of causality. Thrombocytopenia in the neonate can be categorized into fetal, early onset (<72 hours of age), and late onset (>72 hours of age). The most common causes of fetal onset thrombocytopenia are alloimmune, congenital infections (such as with cytomegalovirus, *Toxoplasma*, rubella, and HIV), and aneuploidy (such as trisomies 18, 13, and 21). Less common causes of fetal onset thrombocytopenia are autoimmune, severe hemolytic disease of the newborn, and inherited causes (such as Wiskott-Aldrich syndrome). Because the majority of fetal onset thrombocytopenias present after birth and before discharge from the hospital, only neonatal alloimmune thrombocytopenia (NAIT) is discussed in depth.

NAIT is the platelet equivalent of hemolytic disease of the newborn. NAIT occurs when fetal platelets contain an antigen inherited from the father that is lacking in the mother, resulting in transplacental transfer of maternal IgG antiplatelet antibodies and the ultimate destruction of fetal platelets. Importantly, NAIT can develop in the first pregnancy of an at-risk couple. Because platelet antigens form early in gestation and maternal antibodies cross the placental barrier early in the second trimester, NAIT can result in severe thrombocytopenia.[6] The most common serious side effect of NAIT is intracranial hemorrhage, which can occur in as many as 20% of affected newborns.[7] Nearly 50% of those with intracranial hemorrhage are affected in utero.[8] There is a risk for more severe thrombocytopenia and an increase in the incidence of intracranial hemorrhage in infants affected by NAIT than by autoimmune thrombocytopenia.[9] Antibodies directed against the human platelet antigen-1a (HPA-1a) are responsible for approximately 80% of NAIT in whites. Less than 3% of the white population is homozygous for HPA-1b. HPA-1a incompatibility occurs in 1/150 pregnancies, although thrombocytopenia develops in less than 1/1000 pregnancies.[10] In neonates with NAIT who are neither premature nor ill, thrombocytopenia will resolve in most cases within 1 week without any long-term sequelae. However, in some children, thrombocytopenia lasts for several weeks and may require repeated platelet transfusions. The most important aspect of the management of NAIT is to consider this diagnosis in any case of unexpected severe thrombocytopenia. Prevention of intracranial hemorrhage is an emergency. Term infants who are not ill and have no other risk factors for hemorrhage (eg, traumatic delivery) are transfused using washed and irradiated maternal platelets, or HPA-1a/5b negative platelets, or HPA compatible platelets if available