Case 2: Dropping platelet counts in the neonatal intensive care unit - An unsuspected cause for thrombocytopenia in a neonate

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**Citation of this paper:**  
Wilejto, Marta; Steele, MacGregor; and Jadavji, Taj, "Case 2: Dropping platelet counts in the neonatal intensive care unit - An unsuspected cause for thrombocytopenia in a neonate" (2011). *Paediatrics Publications*. 1661.  
https://ir.lib.uwo.ca/paedpub/1661
Case 2: Dropping platelet counts in the neonatal intensive care unit – an unsuspected cause for thrombocytopenia in a neonate

A premature baby girl born at 28 weeks’ gestation developed thrombocytopenia at approximately 50 days of life (corrected gestational age >35 weeks), which was noted on routine blood work during her admission to the neonatal intensive care unit (NICU).

The mother’s pregnancy history was significant for limited prenatal care. Routine serological testing for rubella, varicella, syphilis, hepatitis B and HIV was not performed, although HIV and hepatitis testing had been normal two years previously. Group B streptococcus status was negative. There was no history of maternal thrombocytopenia. The baby was born at 28 weeks’ gestation via spontaneous vaginal delivery at a peripheral hospital. The infant’s birth weight was 935 g. She was intubated at delivery for low Apgar scores, and transferred to a tertiary care institution for ongoing care.

Ongoing neonatal issues at the time of presentation included a persistent oxygen requirement, apnea and bradycardia of prematurity, and poor growth despite fortified feeds. There were intermittent stools positive for occult blood, but no x-ray evidence of necrotizing enterocolitis or feed intolerance. The patient’s complete blood count had been normal at birth, one week of life and four weeks of life. However, the subsequent test at two months of life revealed normocytic anemia and moderate thrombocytopenia. Given the new finding, empirical treatment with broad-spectrum intravenous antibiotics was started for presumed infection. Platelet transfusion was given with an appropriate, albeit transient rise in platelet count.

Physical examination was remarkable for mild pallor and palpable cervical lymph nodes in an otherwise well-appearing, nondysmorphic, but small-for-corrected gestational age newborn. Investigations including a complete blood count showed normocytic anemia (hemoglobin level 78 g/L); normal white blood cell count with atypical lymphocytes; and a platelet count of 15 × 10^9/L. Platelet reticulocytes were elevated. Liver enzyme levels were mildly elevated, with aspartate aminotransferase 109 U/L and alanine aminotransferase 45 U/L. Echocardiogram and head, abdominal and extremity ultrasounds were unremarkable, with no evidence of thrombus, acute hemorrhage or splenomegaly. Initial infectious work-up, including blood and urine cultures; Epstein-Barr virus serology; urine cytomegalovirus; and hepatitis A, B and C screen, were negative. Rubella serology was indeterminate.

An additional blood test confirmed the diagnosis.
CASE 2 DIAGNOSIS: HIV-RELATED THROMBOCYTOPENIA

The remainder of the infectious work-up revealed that the infant’s HIV serology was positive, suggestive of maternal infection. Further testing was significant for positive HIV-1 DNA via polymerase chain reaction, confirming perinatally acquired HIV infection. Viral load was >3 \times 10^6 \text{ copies/mL}, and CD4 count was 1087 cells/mm^3 (22%). This supported a diagnosis of HIV-related thrombocytopenia.

Neonatal thrombocytopenia: A review

Thrombocytopenia (defined as a platelet count <150 \times 10^9/L) is one of the most common hematological problems seen in the neonatal period, and affects up to 5% of all newborns. In particular, it is frequently encountered in the NICU, where prevalence can be as high as 35%. When approaching a patient with thrombocytopenia, it is often helpful to consider the maternal and perinatal history, physical examination findings as well as timing of onset. The differential diagnosis is broad, and varies depending on early (first 72 h) or later onset (after 72 h) thrombocytopenia, with considerable overlap between the two groups (1). Complications of thrombocytopenia, especially if severe and prolonged, include intraventricular hemorrhage as well as bleeding into other sites. All infants with a platelet count <50 \times 10^9/L (severe) warrant further evaluation.

Within the first days of life, antibody-mediated platelet destruction, intrauterine growth restriction and maternal hypertension (conditions associated with chronic fetal hypoxia) are the predominant causes. Antibody-mediated thrombocytopenia is further classified into neonatal alloimmune thrombocytopenia (maternal antibodies to fetal platelet antigens recognized as foreign) and autoimmune (passive transfer of maternal autoantibodies secondary to maternal disease such as immune thrombocytopenic purpura and systemic lupus erythematosus). Early-onset sepsis and congenital infections may also present in this time period.

Following the immediate neonatal period, sepsis and necrotizing enterocolitis are, by far, the most common causes of thrombocytopenia. Congenital infections such as toxoplasmosis, rubella, cytomegalovirus, herpes simplex virus and syphilis, as well as fungal infections also need to be considered. Other contributors include consumptive processes, such as acute thrombosis or Kasabach-Merritt syndrome, which can be excluded with a detailed physical examination for giant hemangiomata and ultrasonography. Hereditary thrombocytopenias can present at any time in infancy and include amegakaryocytic thrombocytopenia, thrombocytopenia-absent radii and Wiskott-Aldrich syndrome (x-linked recessive, small platelets, atopic dermatitis and immune-deficiency) as well as hereditary macrothrombocytopenias. Finally, metabolic conditions, such as propionic and methylmalonic academia, may also present with a depressed platelet count.

HIV-related thrombocytopenia

Although well-described in the adult literature and in known HIV-positive paediatric patients, HIV-related thrombocytopenia is not commonly considered in the neonatal population. This can be accounted for by multiple factors including reliance on prenatal screening for the infection in expectant mothers, as well as the fact that HIV-associated thrombocytopenia usually does not present in the early neonatal period. However, given the increasing number of women of childbearing age living with HIV infection in developed countries, clinicians should always be aware of this possible diagnosis, especially in high-risk mothers, who may have been screened before seroconversion or who may have gaps in prenatal care. Prolonged stays in the NICU also increase the likelihood that infants will become symptomatic before discharge from hospital. In a baby who presents with persistent, late-onset thrombocytopenia of unknown etiology, congenital HIV infection must be excluded.

Viral infections are believed to result in thrombocytopenia via several mechanisms including loss of sialic acid from platelet membranes (via viral neuraminidase) resulting in increased clearance by the reticuloendothelial system, intravascular aggregation and decreased platelet production (2). The mechanism of thrombocytopenia in the context of HIV is believed to be multifactorial. Contributors include immune-mediated platelet destruction, impaired production of platelets due to bone marrow infection and other HIV-associated conditions such as hypersplenism, opportunistic infections and medication effects (3). Thrombocytopenia usually resolves with highly active antiretroviral therapy. In a subset of patients, however, thrombocytopenia is recurrent and appears to correlate with detectable viral load.

In our patient, antiretroviral treatment was initiated with zidovudine, lamivudine and nevirapine, with a rapid rise in platelet count (254 \times 10^9/L within two weeks of starting treatment) and a brisk CD4 count recovery. Aside from mild persistent cholestasis, her liver enzyme levels normalized and failure to thrive resolved. The child is currently doing well with outpatient highly active antiretroviral therapy.

CLINICAL PEARLS

- Thrombocytopenia in neonates is commonly encountered in the NICU setting. The differential diagnosis is broad and varies depending on the age of the child and the presence or absence of other comorbidities.
- In an infant that presents with persistent thrombocytopenia, a thorough search for an infectious etiology, including congenital infections and HIV, should be undertaken.
- HIV-related thrombocytopenia is often multifactorial and responds to antiretroviral treatment. However, the condition can be persistent or recurrent and, in some patients, correlates with detectable viral load.

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REFERENCES