SHORT COMMUNICATION

Prolonged thrombocytopenia in a child with severe neonatal alloimmune reaction and Noonan syndrome

Inês Salva, Sara Batalha, Raquel Maia, & Paula Kjollerstrom

Department of Pediatric Hematology, Hospital de Dona Estefânia, Centro Hospitalar de Lisboa Central, Lisbon, Portugal

Abstract

Fetomaternal alloimmune thrombocytopenia (FMAIT) caused by maternal antibodies is the leading cause of severe neonatal thrombocytopenia. A 1-month-old Caucasian girl was referred to our Hematology Clinic for persistent thrombocytopenia diagnosed after a bleeding episode. Diagnostic tests suggested FMAIT. Mild thrombocytopenia persisted for 18 months, and subsequent findings of dysmorphic facies, short stature and mild pulmonary stenosis led to the hypothesis of Noonan syndrome (NS), which was confirmed by genetic test. Other hematological abnormalities were excluded and she had no further bleeding episodes. This case illustrates the possibility of different diagnoses with the same clinical manifestations. The persistence of thrombocytopenia longer than expected associated with typical physical features led to the diagnosis of NS.

Keywords

Alloimmune, dysmorphism, neonatal, Noonan syndrome, thrombocytopenia

History

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Introduction

Fetomaternal alloimmune thrombocytopenia (FMAIT) is the leading cause of severe neonatal thrombocytopenia and may cause intracranial hemorrhage (ICH) [1]. It is caused by transplacental transfer of maternal antibodies (anti-HPA), after maternal sensitization to paternally derived antigens, to fetal platelets, most commonly HPA-1a (in 75–90% of cases). Less common antibodies include anti-HPA-5b (10–15%) [1, 2]. When ICH is absent, the prognosis is usually favorable and the platelet count typically recovers to normal values within 8 to 10 days of life [1, 2]. For reasons not well understood, a low count sometimes persists for longer periods of time, occasionally for several months [3].

Case report

One month-old Caucasian girl, second child of a healthy A Rh⁺ mother, presented to our outpatient clinic with a history of persistent thrombocytopenia.

The obstetric history was positive for mild maternal thrombocytopenia during the third trimester (Platelets 119,000/ μ L). The mother was immune to toxoplasmosis and cytomegalovirus, and serologies were negative for other TORCH infections (including syphilis and rubella). The child was born at 37 weeks of gestation, with a birth weight of 3160 g and presented with umbilical cord hemorrhage at birth and multiple ecchymoses. Her physical exam was otherwise unremarkable. Blood tests revealed: hemoglobin 11.7 g/dL, reticulocyte count 8%, leukocytes 16,130/ μ L, platelets 14,000/ μ L, and normal prothrombin time and partial thromboplastin time. During the first 2 weeks of life, platelet counts continued to decrease (minimum of 6000/ μ L on the fourth day of life) despite serial platelet transfusions (1st, 6th, 10th, 11th,

12th, and 13th days of life) and administration of IV immunoglobulin 1 g/kg. Antiplatelet antibody HPA-3b was detected using enzyme-linked immunosorbent assay (ELISA).

The genetic study of the patient showed a 1ab, 2aa, 3ab, 5ab, 4aa, 15ab genotype, while the mother's genotype was 1ab, 2aa, 3aa, 5ab, 4aa, 15ab and the father's genotype was 1ab, 2aa, 3ab, 5aa, 4aa, 15bb. In conclusion, the mother had HPA-3aa platelets, the child HPA-3b platelets, and the cross-match showed that the mother's serum was strongly reactive against the father's platelets. The child was diagnosed with FMAIT. Cranial ultrasound was negative for ICH and her echocardiogram showed only mild pulmonary stenosis.

On the third week of life, her platelet count started to increase to a maximum of 93,000/ μ L. She required a red blood cell transfusion due to anemia (hemoglobin: 9.1 g/dL) on the 25th day of life and was discharged home as she was clinically stable.

The child was referred to our outpatient clinic when she was 1 month old, due to mild and persistent thrombocytopenia despite the absence of episodes of hemorrhage or severe clinical manifestations. During follow-up in the first year of life (with platelet counts 48,000–110,000/ μ L), a dysmorphic facies (high forehead, low set ears, and micrognathia), failure to thrive, and short stature became increasingly apparent, leading to the hypothesis of Noonan syndrome (NS). A mutation in the PTPN11 gene c.181G>A in exon 3 was identified. Further tests for NS—renal ultrasound, thyroid function, coagulation factor assays (V, VII, VIII, IX, X, XI, XII, XIII, von Willebrand), and platelet aggregation as evaluated with PFA 100—revealed no other abnormalities.

She is now 19 months old and has had no further evidence of mucocutaneous bleeding.

Conclusion

NS is a relatively common congenital genetic disorder with an estimated prevalence of 1 in 1000 to 1 in 2500 live births [4]. Characteristic findings include distinctive facial features, short

stature, chest deformity, and congenital heart disease, which may not be apparent during the first months of life and require a high index of suspicion during follow-up [5, 6]. It is an autosomal dominant disorder with complete penetrance but variable expressivity [3]. Mutations in PTPN11 occur in 50% of patients, SOS1 in 13%, RAF in 3–17%, and KRAS in less than 5% [7].

PTPN11 encodes SH2 domain, which contains protein-tyrosine phosphatases Shp1 and Shp2; Shp1 is expressed in hematopoietic and epithelial cells, while Shp2 is expressed widely and they are both key regulators in megakaryocyte development, platelet formation, and function (including interaction with collagen and fibrinogen); these two phosphatases seem to have opposite roles in platelet function (Shp1 reduces platelet response to collagen and fibrinogen by positively regulating immune receptor tyrosine-based activation motif-containing receptors and integrin signaling, whilst Shp2 behaves in the opposite way) [8].

Several hematological abnormalities have been detected in association with this syndrome including thrombocytopenia that may be severe; cases that resemble congenital amegakaryocytic thrombocytopenia have been described and may be caused by specific PTPN11 mutations (c.218C>T) [9, 10]. Although the mechanism responsible for this phenomenon is still incompletely understood, ineffective thrombopoiesis and spleen sequestration are two of the main hypotheses [11, 12]. Other hematological disorders include abnormal platelet function and deficiency of single or multiple coagulation factors (most commonly partial deficiency of factor XI) [4–7, 11–13].

Persistence of thrombocytopenia beyond the second week of life in a child diagnosed with FMAIT should prompt further investigation to exclude other etiologies. In this case, persistence of thrombocytopenia longer than expected associated with dysmorphic facies, pulmonic valve stenosis, developmental delay, and short stature led to the diagnosis of NS. The clinical presentation of severe thrombocytopenia at birth was probably due to the association between the immune mechanism and the congenital cause [14].

This case illustrates the fact that different diagnoses with the same clinical manifestations should be taken into consideration when expected evolution does not occur.

Declaration of interest

The authors report no declarations of interest.

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