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311.DISORDERS OF PLATELET NUMBER OR FUNCTION: CLINICAL AND EPIDEMIOLOGICAL

Two Hit Theory for the Pathogenesis of Type 3 Congenital Amegakaryocytic Thrombocytopenia

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Congenital amegakaryocytic thrombocytopenia (CAMT) is an autosomal recessive disorder characterized by thrombocytopenia with an absence of megakaryocytes. It can lead to aplastic anemia or myelodysplastic syndrome (MDS). CAMT is linked to a mutation in the c-MPL gene on chromosome 1, which encodes the thrombopoietin receptor. In 2005, CAMT was categorized into three types based on the severity of c-MPL gene loss. Type 1 is the most severe, leading to early-onset pancytopenia and bone marrow abnormalities. Type 2 shows a temporary increase in platelets during infancy, followed by bone marrow failure at 3-6 years due to partial gene function. Type 3 has normal c-MPL function but produces ineffective megakaryocytes. We report a case of a patient with CAMT-like symptoms, without a c-MPL gene mutation, suggesting the presence of an alternative genetic defect.

Methods

Multi-institutional collaboration and review of medical records in addition to PubMed search for thrombocytopenia, bleeding complications, macrocytosis, trisomy 6, GATA2 variant, inherited bone marrow failure.

Case Description

A 12-year-old male with severe thrombocytopenia initially observed at 2 years of age. Bleeding complications included scalp hematoma, excessive bleeding during adenoidectomy, widespread petechiae, purpura, epistaxis, and gum bleeding. During this time platelet count ranged between 30-80,000 x10 ^{3}/uL. At 10 years of age, bleeding worsened with platelet counts of 6-20,000 x10 ^{3}/uL. Mean platelet volume (MPV) remained within the normal range. Simultaneously there was a decline in hemoglobin and the emergence of macrocytosis. Mother had moderate thrombocytopenia during pregnancy, older sibling with similar thrombocytopenia but asymptomatic. Clinical presentation made immune thrombocytopenia, autoimmune disorders, and immune dysregulation-induced platelet destruction unlikely. Inherited thrombocytopenia panel testing for 42 germline variants was negative. Bone marrow biopsy showed 60% cellularity and was remarkable for a decrease in megakaryocytes. Cytogenetic analysis revealed trisomy 6 in 7/20 metaphases. Molecular hematopathology identified a GATA2 variant in 50% of the alleles. Inherited BMF panel revealed heterozygosity for multiple variants of unknown significance (VUS), including c.5096A>G (p.Asp1699Gly) in BRCA2 gene, c.3898A>G (p.Ile300Val) in LYST gene, 1408A>G (p.Thr470Ala) in PALB2 gene, and c.7240G>A (p.Val2414Met) in tVPS13B gene. Another BMF panel revealed two additional heterozygous VUS - NBEAL2 and ADAMTS13. Testing for Fanconi anemia and dyskeratosis congenita were negative. Whole exome sequencing revealed heterozygosity for a 1.57 Mb duplication on chromosome 3q29. Additional molecular pathology panel testing for 468 genes, germline genetic testing for lysosomal disorders and mucopolysaccharidoses, were also negative. Repeat bone marrow testing demonstrated a progressive decrease in cellularity to 5-30% with trilineage hypoplasia. With extensive yet inconclusive diagnostic workup, worsening clinical presentation, and progressive hypocellularity of the bone marrow, he underwent an ABO incompatible stem cell transplantation (9:10, A HR) from a mismatched unrelated donor. The conditioning regimen was myeloablative with busulfan, cyclophosphamide, anti-thymocyte globulin, and post-transplant cyclophosphamide. Currently, he is 150 days post-transplant with peripheral blood chimerism demonstrating 97.7% donor on day 98. Platelet counts have normalized, and he has not required a transfusion for nearly 100 days.

Discussion

This case report highlights the concept of a "double hit" hypothesis. While homozygous mutations of PALB2 and BRCA2 are individually associated with Fanconi anemia and BMF syndromes, no hematological pathology has been documented in their

heterozygous forms, raising the question of whether the co-expression of these variants in a heterozygous state could result in a similar disease phenotype as their homozygous counterparts. This finding prompts further exploration into the potential impact of combined variants on disease manifestation.

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