Case Report

Look for the colour: gray platelets – a rare bleeding disorder

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Article Info

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Keywords

Gray Platelet Syndrome, Alpha Granules, NBEAL2, bleeding disorder, ecchymosis

Abstract

Background: Gray Platelet Syndrome (GPS) is a very rare bleeding disorder. It is characterised by mild to moderate bleeding with macro thrombocytopenia and impaired alpha granules in megakaryocytes and platelets.

Case Details: A 8-year-old boy, presented with ecchymotic patches all over the body since early childhood. On examination, he had ecchymotic patches over the thigh and back. There were no dysmorphic features, lymphadenopathy or hepatosplenomegaly. Hemogram showed borderline low platelet (1.1*10^9) and normal hemoglobin and leucocytes. Prothrombin and Partial thromboplastin time were normal. Peripheral smear showed large platelets that lacked granules and looked pale, prompting us to think of Gray Platelets Syndrome. Mean platelet volume was 12.8fL. Genetic sequencing revealed homozygous mutation in the exon35 of NBEAL2-(c.5597del) gene, confirming the gray platelet syndrome (GPS).

Conclusion: High index of suspicion and coordinated care between clinician and pathologists are important for timely diagnosis of such rare disorders.

Background

Inherited thrombasthenia syndromes present with mucocutaneous bleeds and normal to borderline platelet count. Because of the rarity, there are often delays in diagnosis in view of near normal platelet count. Gray Platelet Syndrome (GPS), one of the rarest disorders and sparsely reported worldwide, is a rare macro thrombocytopenia with impaired alpha granules in megakaryocytes and platelets [1].

Clinical Diagnostic Case

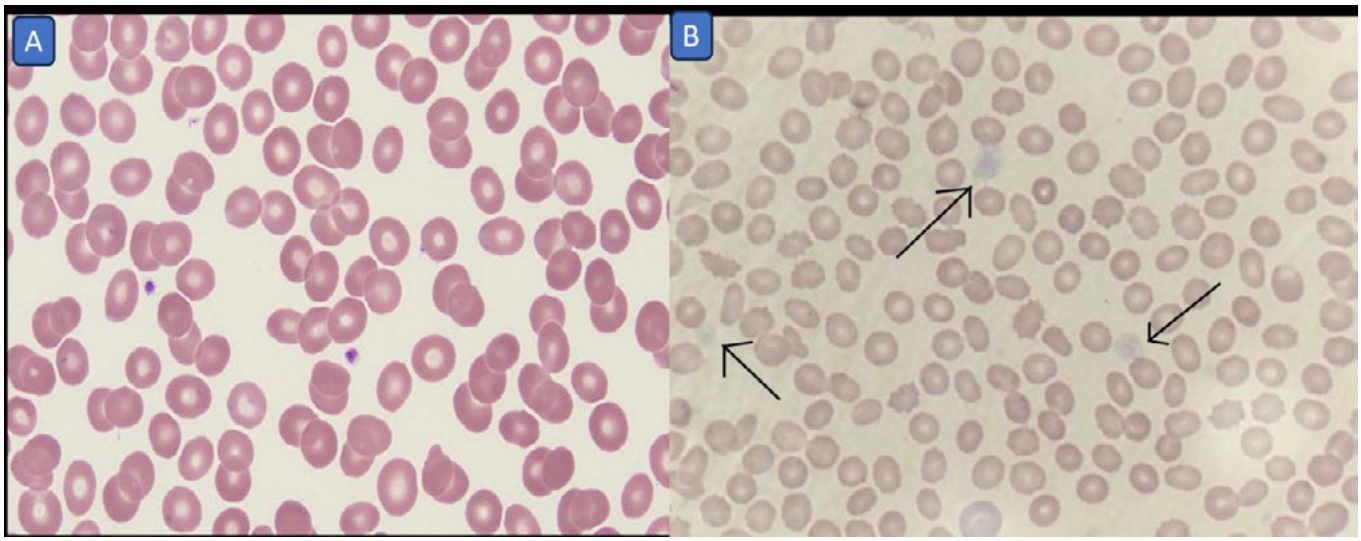
T, 8-year-old boy, born to a third- degree consanguineously married couple, presented with ecchymotic patches noted all over the body, since he was a toddler. There was no history of excessive bleed after fall of umbilical cord or tooth fall. Boy had sustained a lip laceration after trauma, when he had prolonged mild oozing, which was managed with conservative measures. Parents have never sought any medical attention till date as the bleeds were not significant enough to affect his quality of life.

His mother also reported similar ecchymotic patches present intermittently, for which she has never sought any medical attention. There was history of excessive postpartum bleeds after second delivery, when she required blood transfusion and recovered. subsequently, not evaluated further, as baby didn't have any significant bleeds.

On examination, the boy had ecchymotic patches over the thigh and back. There was no dysmorphism, external malformations, lymphadenopathy or hepatosplenomegaly.

Complete blood count showed mild thrombocytopenia (1.1*10^9) and normal hemoglobin and leucocytes. Prothrombin and Partial thromboplastin time were normal. Peripheral smear done with Wrights Giemsa stain showed large platelets that lacked granules and looked pale (Figure 1), prompting us to think of Gray Platelets Syndrome.

Figure 1: A: normal peripheral smear showing normal platelets, B: Peripheral smear stained with wright Giemsa stain 1000x showing giant colorless platelets.



Peripheral smear stained with wright Giemsa stain 1000x. (in the manuscript).

Mean platelet volume was 12.8fL. Vitamin-B12 levels were elevated (>2000pg/ml). Platelet aggregometry revealed low aggregation with epinephrine and Ristocetin; aggregation with adenosine diphosphate (ADP) and arachidonic acid (AA) were normal. Complete coagulation profile with Von-Willebrand antigen factor assay was normal. Genetic sequencing revealed homozygous mutation in the exon35 of NBEAL2-(c.5597del) gene, confirming the gray platelet syndrome (GPS). Parents have been counselled about the implications, precautions to avoid trauma, non-steroidal anti-inflammatory drugs, contact sports and necessary lifestyle modifications and need for long term clinical follow-up with periodic follow-up.

Discussion

Gray Platelet Syndrome (GPS) is a rare bleeding disorder. It is inherited in autosomal recessive or dominant manner. Prevalence has been less than 1 case in 1 million population [2]. The first report of GPS was described by Raccuglia in 1971, as a qualitative platelet defect in a boy with skin bleeds noted since neonatal period [3].

It is a form of alpha granule deficiency where platelets lack alpha granules and their content which is a pathognomonic finding. Platelet consists of various types of granules such as alpha granules, dense granules and lysosomes of which alpha granules are the most abundant. These alpha granules are spherical organelles with dense nucleoid which constitute 1-15% of total

platelet volume. These alpha granules contain variety of proteins such as P-Selectin and fibrinogen, which would involve various functions such as inflammation, hemostasis and wound healing [4,5].

Platelets characteristically appear gray in colour hence named as GPS. Platelets in GPS also frequently display prominent vacuolization of the cytoplasm, with preservation of content of dense granules, mitochondria, lysosomes and peroxisomes. Nurden aet al suggested that GPS is a heterogeneous syndrome with GP6 deficiency and reduced levels of platelet membrane TLT1, which is located in the membrane of alpha-granules, and reduced levels of P-selectin. In contrast, there was another report of a patient with GPS with normal collagen-induced platelet aggregation and normal levels of GP6, TLT1, and P-selectin, suggesting biochemical, phenotypic, and molecular heterogeneity in GPS [6].

Clinical presentation includes mild to moderate bleeding, splenomegaly, progressive myelofibrosis and elevated B12 levels. It is characterized by macro-thrombocytopenia [2]. Recurrent infection and autoimmune diseases such as Hashimoto thyroiditis and atypical autoimmune lymphoproliferative syndrome are also a part of spectrum of presentations of GPS. Bone marrow examination reveals extensive emperipolesis of neutrophils within megakaryocytes.

Patients with GPS showed a defective PAR1-mediated platelet response, either isolated or combined to defective responses to other agonists and is paralleled by reduced expression of PAR1 on the platelet surface [3].

In patients with GPS, the platelet aggregation defects are heterogeneous [7,8]. In a study done by Hayward et al in GPS patients showed that about 50% of patients showing an impaired platelet response to collagen [9]. In a case series of 8 patients with GPS reported by Mori et al, showed decreased platelet aggregation with ADP, collagen, Ristocetin and epinephrine [10].

GPS is caused by pathogenic variants in neurobeachin-like 2 (*NBEAL2*), which encodes a protein important in alpha granule biogenesis. This gene is mapped to chromosome 3p21. This gene is a member of the family of beige and Chediak-Higashi (BEACH) genes.
Pathogenic variants in *GFI1*, which encodes for transcriptional repressor active in megakaryocytes, have also been described to cause GPS.
Most common mode of transmission is autosomal recessive for the NBEAL2-related form and rarely autosomal dominant for the GFI1B-related form [11,12].

GPS spans across various cell lineages beyond megakaryocyte-platelet, involving the innate and adaptive immune system, thereby widening its phenotypic spectrum. Neutrophils can also be degranulated with a grayish appearance on the blood smear. However, despite these structural defects, no functional abnormalities are evident in neutrophils [13,14].

Treatment of most patients with GPS is based upon the severity of bleeding. Bleeding may occur spontaneously or following a trauma. Measures such as anti-fibrinolyics, avoidance of NSAIDs, and blood transfusions are helpful. Role of Eltrombopag in GPS is unknown [15].
Stem cell transplant may offer a promising curative option in patients with GPS with refractory bleeds [16].

Apart from bleeding diathesis, disease is associated with myelofibrosis, splenomegaly and rarely, defects in adaptive immune system. Though this diseases is associated with , it can also be acquired in patients with myeloproliferative neoplasm (MPN) especially in adult patients. When morphologically unusual platelets are observed in patients with such neoplasm, platelet dysfunction disorders such as acquired GPS, should be ruled out [17].

Take Home Messages

High index of suspicion, good quality peripheral smear examination and coordinated care between clinician and pathologists are important for timely diagnosis of such rare disorders. Further research in pathogenesis of GPS and effects of NBEAL2 mutations would provide important tools for developing appropriate therapy.

Disclosures

The authors have no relevant financial or non-financial interests to disclose. The authors have no competing interests to declare that are relevant to the content of this article.

Conflicts of Interest

None.

Declaration of Helsinki

The study is in compliance with the ethical principles for medical research involving human subjects, in accordance with the Declaration of Helsinki.

Author contributions

YJG, RB, AT and DJ worked on the data analysis and wrote the initial draft; DJ, JXS and SG revised it for the clinical content and final revision for intellectual content by DJ and JXS. All the other authors were involved in the management of the child. All authors read and approved the final manuscript.

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