Understanding and Managing Inherited Platelet Disorders: A Case Study of Storage Pool Disease

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Abstract: Inherited platelet disorders, including platelet storage pool diseases (SPDs), manifest in various bleeding symptoms, with severity often categorized based on their effects on either the surface receptors or internal structures of platelets [1]. This rare condition, characterized by defects in platelet granules, exhibits broad phenotypic variability, ranging from mild bruising to severe hemorrhages. Diagnosis involves specialized analyses such as platelet aggregation and genetic studies, necessitating a multidisciplinary approach for management [2]. Our case report describes a child with recurrent epistaxis, initially diagnosed with immune thrombocytopenia. Subsequent presentations led to suspicion of von Willebrand disease, but further examinations revealed a platelet function disorder. Genetic testing confirmed mutations associated with SPD. Treatment options include desmopressin, antifibrinolytic agents, and platelet transfusions, tailored to individual needs. The discussion underscores the diverse manifestations of SPD, emphasizing the importance of thorough diagnostic assessments. Treatment strategies aim to alleviate bleeding symptoms and mitigate associated risks, with a strong focus on personalized care. Challenges in managing SPD include missed diagnoses and the influence of genetic variations on disease severity. Ultimately, early detection and individualized therapies are essential for effectively managing SPD, underscoring the ongoing need for research to enhance outcomes for affected individuals.

Keywords: Bleeding, Desmopressin, Platelet defects, Inherited platelets disease, Tranexamic acid, Platelet transfusion, Storage Pool Disease.

INTRODUCTION

Inherited platelet disorders manifest with a spectrum of bleeding symptoms that vary in severity. These abnormalities are classified into disorders affecting either the surface receptors or the internal structures of platelets. Among the latter group are platelet storage pool diseases (SPDs), characterized by defects in platelet granules. Depending on the specific granules affected-α-granules, δ-granules, or both-the clinical presentation can differ, leading to conditions such as α-SPD (*e.g.*, Gray platelet syndrome, Quebec platelet disorder, arthrogryposis, renal dysfunction, and cholestasis syndrome), δ-SPD (*e.g.*, Hermansky-Pudlak syndrome, Chediak-Higashi syndrome, Griscelli syndrome), or αδ-SPD (*e.g.*, X-linked thrombocytopenia, Wiskott-Aldrich syndrome) [1, 3]. This relatively rare condition exhibits broad phenotypic variability and can result in bleeding symptoms ranging from mild bruising to severe hemorrhages, significantly affecting patients' quality of life. Diagnosing SPD is complex and typically involves specialized analyses such as platelet aggregation, flow cytometry, and genetic studies [4]. The management of these disorders often necessitates a multidisciplinary approach involving hematologists, surgeons, and other specialists to ensure proper symptom management and mitigate associated bleeding risks. While many of these disorders may respond to similar treatment approaches, the effectiveness of interventions can vary among individuals. Treatment strategies may encompass medications such as tranexamic acid, desmopressin (DDAVP), activated factor VII (FVIIa), and platelet transfusions. In severe cases, consideration may be given to stem cell or bone marrow transplants [5].

CASE REPORT

A three-year-old child had a history of recurrent episodes of profuse epistaxis. There were no other signs of spontaneous excessive bleeding, the family history was negative for known coagulopathies. In October 2021, following repeated episodes of epistaxis at home, the patient was for the first time admitted to the ER, a Complete Blood Cells Count (CBC) showed

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thrombocytopenia (PLT count= 33x 10^9 /L), he was than referred to a Pediatric Oncohematology Unit where he underwent bone marrow aspirate, showing no abnormalities with the exception of an imbalanced myeloid/lymphoid ratio in favor of the lymphoid fraction. The patient was treated with intravenous immunoglobulins in response to the diagnosis of immune thrombocytopenia, resulting in an increase in platelet count. In March 2022, epistaxis recurrent and a further reduction in platelet count was observed (PLT count=14 x 10^9 /L) so the child was admitted again to the ER. Once there he was successfully treated with intravenous immunoglobulins, resulting in epistaxis control and normalization of the platelets count , leading to a diagnosis of relapsed immune thrombocytopenia.

In June 2022, the patient presented to the pediatric ER due to the onset of diffuse petechiae of the four extremities throughout the body. During hospitalization, melena also occurred, prompting a complete abdominal ultrasound examination, revealing both centimetric and subcentimetric lymph nodes in the paraumbilical region, hepatomegaly with a homogeneous liver echostructure, and splenomegaly with a diameter of approximately 7.8 cm. Given the worsening of hemorrhagic lesions, a CBC follow-up was performed, revealing the following: white blood cell count(WBC) of 6,63 x 10^9 /L with preserved differential count, hemoglobin level of 12.8 g/dl, MCV of 72.2 fl, and platelet count of 172 x 10^9 /L. The patient was admitted to the Meyer Hospital in Florence and based on laboratory findings during hospitalization, hematologic consultation was requested due to the suspicion of von Willebrand disease.

In July 2022, the patient came to our attention for further investigations with the following results: the vW:Ricof (73%), vWF:Ag (68%), with F:RCo/Ag (1.08), and FVIII (110.2%), patient's blood type was A Rh +, so a diagnosis of von Willebrand disease was thus ruled out. However, based on the patient's clinical history, additional examinations were performed, including a light transmission aggregometry (LTA), which showed marked inhibition of platelet aggregation to ADP, epinephrine, and arachidonic acid, thus suggesting a platelet function disorder. Flow cytometry also ruled out Glanzmann thrombasthenia (GT) and Bernard Soulier syndrome (BSS). In November 2022, the patient was again admitted due to moderate thrombocytopenia secondary to an episode of fever and inflammation of the upper respiratory tract, with a reported platelet count of 50 x 10^9 /L, in the absence of hemorrhagic symptoms. At that time for further diagnostic completion, samples were sent to a highly specialized laboratory for genomic analysis.

While the results of the genetic tests were still pending, the patient was hospitalized again in January 2023 due to petechiae and thrombocytopenia (PLT count= 25 x 10^9 /L). He was again treated with intravenous immunoglobulin therapy at a dose of 0.8 mg/kg, resulting in an Improved platelets count. He was subsequently discharged with a PLT count of 174 x 10^9 /L,in the absence of any bleeding symptoms.

In February 2023, IInd level platelets assays were extended to first-degree relatives, particularly conducting LTA:

- 15-month-old sister: The test revealed a predominantly functional defect in response to ADP and epinephrine stimuli, consistent with the brother's platelet release disorder;
- 25-year-old mother: Investigations did not reveal alterations in platelet function;
- 33-year-old father: A functional defect in response to ADP and epinephrine stimuli, although clinically silent, was observed, consistent with the son's platelet release disorder

Excluding the diagnosis of Glanzmann thrombasthenia and Bernard-Soulier syndrome , the child's sample was referred to a second-level facility for the diagnosis of rare platelet disorders. Based on the clinical and laboratory characteristics, as well as the results of the genetic study revealing mutations in ANKRD26, ITGA2B, ITGB3, a diagnosis of “storage pool disease” was established.

DISCUSSION

"Storage pool disease" (SPD) is a condition belonging to the category of Platelet diseases, which, although rare, represent the third leading cause of hemorrhagic blood disorders. Therefore, once more common bleeding conditions have been ruled out through specific tests, these less common conditions should always be investigated and potentially ruled out as well [6]. Storage pool disease encompasses a diverse range of congenital disorders characterized by a common deficiency in platelet granules or their components. The absence of platelet granules leads to impaired secretion, such as deficient release of ADP from activated platelets, and abnormal platelet

aggregation dependent on secretion [7]. Platelet granules are categorized into α-granules and δ-granules (dense bodies). α-granules serve as storage sites for proteins synthesized in megakaryocytes (MKs) or taken up from the plasma. They contain various proteins involved in platelet adhesion (*e.g.*, von Willebrand factor (VWF), P-selectin, fibronectin, fibrinogen), coagulation factors (*e.g.*, factors V and XIII), growth factors (*e.g.*, platelet-derived growth factor, transforming growth factor-β), and platelet factor-4. On the other hand, δ-granules predominantly contain calcium, ATP, ADP, serotonin, histamine, and epinephrine. Based on the deficiency of α-granules, δ-granules, or both, and their specific contents in platelets, the clinical syndrome is classified as α-SPD, δ-SPD, or combined αδ-SPD [8]. These disorders, affecting the extension phase of clot formation, are associated with impaired platelet function, as evidenced by reduced aggregation responses.

To diagnose SPD, various diagnostic methods can be used, including signs and symptoms analysis (signs of excessive bleeding, such as easy bruising, frequent nosebleeds, gum bleeding, gastrointestinal bleeding, or hematuria); laboratory tests (platelet count platelet function, and analysis of platelet morphology, platelet aggregation and serotonin release can be used to assess platelet function); genetic studies, infact DNA analysis may be performed to identify specific genetic mutations associated with the disease [1]. Since symptoms of platelet storage pool disease may overlap with those of other bleeding disorders, it is important to exclude other causes of excessive bleeding through a comprehensive evaluation of clinical history and laboratory test results. The treatment of these conditions frequently requires a collaborative effort involving hematologists, surgeons, and other experts like otolaryngologists (ENT) to effectively address symptoms and reduce the potential risks of bleeding. In cases where patients present with symptoms such as epistaxis (nosebleeds) or oral bleeding, ENT specialists may be involved in evaluating and managing these symptoms.There are three main treatment options for patients with platelet storage pool disorders in cases of severe bleeding, or in anticipation of surgical interventions:

- L-deamino-8-darginine vasopressin (DDAVP), also known as desmopressin,
- ε-antifibrinolytic agents like aminocaproic acid, and
- platelet transfusions.

The choice of treatment depends on various factors such as the patient's response, the extent of the surgical procedure, and the potential risks associated with bleeding [1, 9]. For patients with mild conditions, DDAVP is preferred over blood products. It can be administered intravenously, subcutaneously, or intranasally, with the intravenous route commonly chosen for perioperative care. The recommended dose is 0.3 μg/kg over 60 minutes to prevent hemodynamic effects such as hypotension. DDAVP works by increasing the release of von Willebrand factor antigen and Factor VIII, enhancing platelet aggregation without affecting platelet count. For minor surgeries, desmopressin can reduce the need for blood products, with potential mild adverse effects including tachycardia, headache, flushing, and fluid retention. Anti-fibrinolytic agents such as ε-aminocaproic acid or tranexamic acid are effective in preventing bleeding, especially in surgeries involving areas rich in proteolytic enzymes like the oral cavity and otolaryngology. These agents prevent clot degradation by inhibiting the conversion of plasminogen to plasmin. They are available in intravenous and oral forms, with common side effects being gastrointestinal symptoms that usually resolve with dose adjustment. Thrombotic events are rare, especially in pediatric patients. In severe cases or major surgeries, additional therapies alongside DDAVP and antifibrinolytic agents may be necessary, including platelet transfusions [5].

CONCLUSIONS

The case illustrates the diagnostic and therapeutic challenges in managing patients with bleeding disorders, highlighting the importance of detailed and up-to-date investigations for accurate diagnosis and targeted therapy. Inherited platelet disorders should be suspected in patients with a history of bleeding despite negative initial tests. Due to the rarity of the condition and the specialized tests required for diagnosis, unfortunately, there are many missed diagnoses, and even when the diagnosis is made there are genetic variations that are difficult to identify but still influence individual vulnerability and the severity of the condition. To summarize, this case highlights the importance of identifying and effectively managing Storage Pool Disease to enhance the quality of life of affected individuals. It also stresses the significance of early detection and personalized therapies to improve clinical results and mitigate hemorrhagic risks. Further research is imperative to completely grasp the underlying pathogenic mechanisms and devise more efficient treatments for this uncommon yet consequential bleeding disorder.

PATIENTS CONSENT

Parents signed an Informed Consent for the management of personal and clinical data for health services and research purposes, as per policy of the Center, at the time of first visit at our outpatient clinic.

CONFLICTS OF INTEREST

The authors declare no conflicts of interest.

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