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Joana M. Mack *

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Research Article

Severe Menorrhagia and Thrombocytopenia in a Patient with Pseudohypoparathyroidism

Short title: Patient with AHO and bleeding

Lily Suh M.D.[1,2], Emily Beckett D.O.[1,2], Jason E. Farrar M.D.[1,2], Cristyn Branstetter M.D.[3], Joana M. Mack M.D.[1,2]
[1]Department of Pediatrics, Division of Pediatric Hematology-Oncology, University of Arkansas for Medical Sciences.
[2]Arkansas Children's Hospital.
[3]Arkansas Children's northwest.
***Corresponding Author:** Joana M. Mack, Department of Pediatrics, Division of Pediatric Hematology-Oncology, Arkansas Children's Hospital, University of Arkansas for Medical Sciences, Little Rock, Arkansas, USA.

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Abstract

A 15-year-old female with a history of hypothyroidism presented with severe anemia and thrombocytopenia in the setting of prolonged menses. After further evaluation, she was diagnosed with pseudohypoparathyroidism Ia (PHPIa). Her symptoms improved after starting medications and receiving a platelet transfusion, but a few weeks later she returned with complaints of bleeding and dizziness and was found to be thrombocytopenic once again. Her platelet counts improved after administration of intravenous immunoglobulin (IVIG), leading us to believe she has a combined immune mediated platelet destruction in addition to platelet dysfunction associated with her PHPIa.

Keywords: bleeding; immune thrombocytopenic purpura; albright hereditary osteodystrophy

Abbreviations:

PHPIa	Pseudohypoparathyroidism Ia
IVIG	Intravenous Immunoglobulin
PTH	Parathyroid Hormone
TSH	Thyroid Stimulating Hormone
LH	Luteinizing Hormone
FSH	Follicle Stimulating Hormone
AHO	Albright Hereditary Osteodystrophy
BMI	Body Mass index
Ca	Calcium
PT	Prothrombin Time
PTT	Partial Thromboplastin Time
INR	International Normalized Ratio
LDH	Lactate Dehydrogenase
IgG	Immunoglobulin G
ANA	Antinuclear Antibody
CAMP	Cyclic Adenosine Monophosphate
GPCR	G-Protein Coupled Receptor
ITP	Immune Thrombocytopenic Purpura

Introduction

Pseudohypoparathyroidism Type 1a (PHP) is a genetic disorder characterized by an inactivating mutation of the alpha subunit of a GNAS encoded G-protein, resulting in end organ resistance to parathyroid hormone (PTH). Therefore, the usual laboratory findings include hyperphosphatemia, hypocalcemia and elevated PTH. Patients can also show end-organ resistance to other hormones, including thyroid stimulating hormone (TSH), luteinizing hormone (LH), and follicle stimulating hormone (FSH), and have phenotypic features typical of Albright Hereditary Osteodystrophy. Bleeding complications, however, are not commonly associated with the diagnosis [1].

We present a case of 15-year-old female with a history of hypothyroidism and easy bruising who presented with severe anemia and thrombocytopenia in the setting of prolonged menses. While her labs and physical appearance were typical of PHPIa/AHO, this case is notable for an atypical presentation and rare association with thrombocytopenia not previously reported in the literature.

Methods

Chart and literature review.

Case Presentation

A 15-year-old female with a history of hypothyroidism and easy bruising presented with syncope in the setting of uncharacteristically prolonged and heavy menses. Menarche occurred at 14-years-old with increasingly irregular cycles over the last year. She had a history of easy bruising but no significant history of bleeding and had never required a blood transfusion.

She was previously diagnosed with hypothyroidism but had been lost to follow up. There was no family history of bleeding disorders, endocrinopathies or any other genetic predispositions. Her physical exam was notable for pallor, round facies, shortened 4th metacarpals and metatarsals (Figures 1 and 2), a subcutaneous calcification of her right thigh and scattered bruising over all extremities and chest. Additionally, her BMI was 32 kg/m^2 and her height persistently tracked below the 10th percentile since childhood.

Figure 1

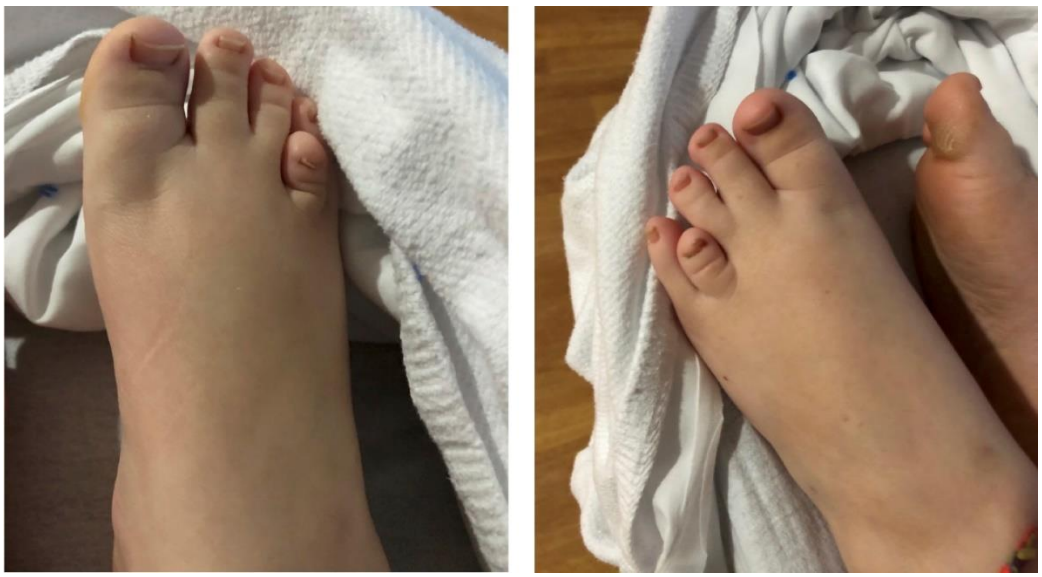

Figure 2

Initial bloodwork showed profound anemia (hemoglobin 7.3 g/dl) and thrombocytopenia (Platelet count 15 K/uL), significant hypocalcemia (Ca 5.1 mg/dl), and hyperphosphatemia (Phosphorus 7.2 mg/dl). PTH was markedly elevated (PTH 518 pg/ml) while Vitamin D was within normal limits. TSH was elevated (19 mIU/L) with normal Free T4. PT/PTT/INR, uric acid, LDH, bilirubin levels, and von Willebrand studies were normal. Platelet antibody testing was sent with eventual results of strongly positive anti-platelet antibody IgG. She received 20ml/kg of packed red blood cells and was started on norethindrone for menstrual suppression. She also received 5ml/kg of platelets and demonstrated subsequent steady increase in her platelet count until discharge.

We made a presumptive diagnosis of Pseudohypoparathyroidism (PHP)/Albright Hereditary Osteodystrophy (AHO) following endocrinology consultation due to exam findings and abnormal laboratory evaluation. She was started on levothyroxine, calcium carbonate and calcitriol. An AHO genetic test looking for mutations in the coding regions of GNAS1 gene sent during the admission returned negative;

however, the testing methodology is not comprehensive for all mutations and she still has a presumed diagnosis of PHPIa/AHO.

Several weeks after initial presentation, she presented to an outside hospital, again with dizziness, menorrhagia and thrombocytopenia (Platelets 11 K/uL). She received 2 transfusions of platelets with initial increase then subsequent drop in platelet counts. Her platelet count rebounded after treatment with 1g/kg of IVIG. Considering her response to the IVIG and her history of positive anti-platelet antibodies she was diagnosed with immune thrombocytopenia.

On her first follow up in hematology clinic two months after initial presentation, she was asymptomatic but once again had a low platelet count (19 K/uL). However, five months after initial presentation, she complained of recurrence of heavy menstrual bleeding, fatigue and dizziness associated with thrombocytopenia (Platelets 13 K/uL). Further bloodwork including ANA and immunoglobulin levels resulted with normal values. Due to her atypical presentation and potential need for steroids or immunosuppressants, a bone marrow sample was taken with normal cellularity and platelet precursors without evidence of leukemia, myelodysplastic syndrome or bone marrow failure. She was subsequently started on eltrombopag (Promacta). Since then, she has maintained her platelet count > 50 K/uL and has not had further bleeding symptoms.

Review of the Literature

Pseudohypoparathyroidism 1a (PHPIa) was first associated with inactivating mutations of the GNAS gene in 1990 [1]. Since then, there have been hundreds of mutations identified within the GNAS gene in patients with PHPIa including but not limited to point mutations, frameshift mutations, and insertion/deletion mutations [2]. However, the different types of mutations have not yet been linked to significant differences in the disease onset, symptoms, or severity [1]. Studies found that inactivating GNAS mutations are not detectable in up to 40% of patients with PHPIa [3, 4].

Because platelets are easily accessible and the role of G-protein coupled receptors (GPCR) is well understood in terms of platelet function, they have been the center of study for mutations in GPCR in diseases like PHPIa [2, 3]. PHPIa is attributed to a maternally inherited autosomal dominant mutation of GNAS that in turn leads to hypofunctioning of the Gs-alpha protein in cell signaling [1, 4]. This is demonstrated by platelet aggregation inhibition tests that show decreased amounts of second messenger (cAMP) generation after incubation with varying amounts of Gs alpha agonists (ie Prostacyclin or prostaglandin E2) in those with PHPIa [3, 5, 6]. While megakaryocytes also express GPCR, their role in megakaryopoeisis is poorly understood, making the effect of mutations difficult to determine.

PHPIa is a rare diagnosis associated with end organ resistance to parathyroid hormone and potentially other hormones (thyroid stimulating hormone, growth hormone releasing hormone, gonadotropins), as well as physical features of Albright Hereditary Osteodystrophy (brachydactyly, subcutaneous ossifications, round facies, obesity, short stature, intellectual disability) [1, 2, 4, 6, 7]. However, the diagnosis is not widely associated with bleeding or thrombocytopenia. In fact, a case report done in 2008 associates the diagnosis with prothrombotic states, attributed to the profound hypofunction of the Gs alpha subunits in platelets which leads to decreased cAMP and increased aggregation [6].

While there are several studies to suggest that an activating mutation of Gs-alpha, present in McCune Albright Syndrome, could be associated with bleeding tendencies, few such findings have been reported in the case of PHPIa. In this review, no previous studies were found relating teenage females with PHPIa with menorrhagia or history of easy bruising/bleeding. The only reported instances of bleeding or thrombocytopenia with PHPIa diagnosis were in infant or toddler aged children who, similar to this patient had concomitant diagnoses that may explain a low platelet count. For example, in 2008, Pavone et al published a case report outlining a 3-year-old with PHPIa diagnosed as an infant, who later developed Evans Syndrome (disorder characterized by having both autoimmune hemolytic anemia and idiopathic thrombocytopenic purpura). He presented with anemia, thrombocytopenia and splenomegaly but, unlike our patient, did not have any acute bleeding [7]. After his bone marrow biopsy was found to be normal, he was treated with IVIG, cortisone and clarithromycin with subsequent resolution of anemia and thrombocytopenia. Another case study published in 2009 questioned the relationship of trauma related bleeds to PHPIa in a 6-month-old diagnosed with PHPIa who died after significant hemorrhagic cerebral infarcts and DIC following neurosurgery to correct severe craniosynostosis. Postmortem studies identified GNAS mutation in the infant without any other identifiable cause of platelet dysfunction [8]. Finally, there are studies that associate increased bleeding tendencies in those with polymorphisms of XLalphaS, the paternally expressed isoform of GNAS [3, 5]. However, PHPIa results from maternally inherited GNAS mutations [1, 2, 3, 4, 6].

Menorrhagia, anemia and thrombocytopenia, therefore, are atypical symptoms, seldom reported upon in those with PHPIa, and therefore make this case quite unique.

Discussion

PHPIa is a diagnosis made based both on clinical features and laboratory findings, but without notable issues regarding platelet count or function [1]. Therefore, bleeding and thrombocytopenia are atypical presenting signs/symptoms of PHPIa, with few cases reported in the literature. Based on current understanding of the function of G protein coupled receptors in platelet activation, it may seem more likely that inactivating mutations of Gs-alpha (such as the GNAS mutation seen in PHPIa) could lead to prothrombotic states due to decreased second messenger activity and subsequent increased platelet aggregation, however, this is not regularly seen in children with PHPIa [3]. Of the few reported cases of children with PHPIa and associated bleeding, the patients were younger than our patient and had secondary diagnoses that likely explain the hematologic findings.

Our patient presented with classic signs and symptoms of PHPIa including physical findings of round facies, calcifications and shortened 4th digits as well as bloodwork concerning for end hormone resistance to PTH and TSH. However, unique to her presentation was the menorrhagia and subsequent findings of profound anemia and thrombocytopenia. Because she responded so well to PRBC transfusion and platelet transfusion during her first presentation, we initially suspected platelet dysfunction with a mild thrombocytopenia that was worsened by her acute and significant menstrual bleeding. However, after discharge, she presented several more times with low platelet counts and bleeding, which significantly improved only after IVIG infusion and starting eltrombopag, a thrombopoietin receptor agonist indicated for use in persistent/chronic ITP. These findings, in conjunction with the anti-platelet antibodies found on initial workup, more strongly suggest that the etiology of her thrombocytopenia is autoimmune in nature, but because she responded so rapidly to a single platelet transfusion on her first admission, we cannot rule out that she has a combined issue of platelet dysfunction and platelet destruction.

This case adds to the small number of cases relating bleeding/thrombocytopenia in patients diagnosed with PHPIa and highlights the continued need for vigilance in determining the potential relationship between the two.

Conclusions

PHPIa is seldom associated with bleeding and thrombocytopenia. While there is research being conducted on the effect of mutations affecting Gs-alpha proteins on platelet function, the way this translates into clinical presentations of patients with PHPIa is still unclear. Therefore, it is important to consider concurrent diagnoses such as ITP in the setting of bleeding and thrombocytopenia, as seen in our patient who responded well to IVIG infusion.

Conflict of Interest

The authors declare that there is no conflict of interest.

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