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CASE REPORT

Coexistence of Immune Thrombocytopenic Purpura and Bernard-Soulier Syndrome: A Rare Pediatric Case Report

Sondus Alsharidah, Eman Almatar, Rania Lutfi, Omnia A Hashem

Department of Hematology, NBK Specialized Children's Hospital, Sabah, Kuwait

Correspondence: Eman Almatar, Department of Hematology, NBK Specialized Children's Hospital, Sabah, Kuwait, Tel +965 99059297, Email er.almatar@gmail.com

Background: Immune thrombocytopenic purpura (ITP) is an autoimmune disorder characterized by low platelet counts, typically presenting with mucocutaneous bleeding. Bernard-Soulier Syndrome (BSS) is a rare inherited platelet disorder associated with thrombocytopenia, giant platelets, and impaired platelet function.

Case Report: We present the case of an 8-year-old girl presenting with recurrent epistaxis, mucosal bleeding, and thrombocytopenia. Genetic analysis revealed a heterozygous germline *ETV6* mutation associated with thrombocytopenia and leukemia risk, and a *GP1BB* mutation diagnostic of BSS. She was managed with intravenous immunoglobulin (IVIG) and corticosteroids; Eltrombopag was discontinued due of leukemic risk. The patient's platelet counts stabilized with supportive management and she remains clinically stable without recurrent severe bleeding.

Conclusion: The purpose of this case report is to illustrate the diagnostic challenges and therapeutic considerations in children with coexisting acquired (ITP) and inherited (BSS) thrombocytopenias, particularly in the presence of a leukemogenic predisposition gene (*ETV6*). This case underscores the importance of comprehensive genetic evaluation in guiding individualized therapy and long-term surveillance.

Keywords: immune thrombocytopenic purpura, ITP, Bernard-Soulier syndrome, BSS, ETV6 mutation, GP1BB mutation, genetic testing, pediatric bleeding disorder

Background

Immune thrombocytopenic purpura (ITP) is an acquired autoimmune disorder characterized by immune-mediated platelet destruction and impaired megakaryopoiesis, resulting in thrombocytopenia despite normal bone marrow morphology.[1–5] It primarily affects primary hemostasis and clinically presents with mucocutaneous bleeding, including purpura, epistaxis, ecchymoses, menorrhagia, and hematuria, although some patients may remain asymptomatic.[3,6,7] The annual incidence of ITP in children is estimated at 4–6 per 100,000 per year.[6]

Bernard-Soulier syndrome (BSS) is an inherited platelet disorder caused by mutations affecting the GPIb-IX-V complex, a receptor critical for von Willebrand factor-mediated platelet adhesion. Dysfunction or absence of this receptor results in macrothrombocytopenia, impaired platelet adhesion, prolonged bleeding time, and a heightened risk of severe mucocutaneous bleeding.[7,8] Unlike ITP, BSS is extremely rare, with a prevalence estimated at fewer than per million individuals worldwide.[8]

The coexistence of an acquired thrombocytopenia such as ITP and an inherited platelet disorder such as BSS is rare and diagnostically challenging, as overlapping clinical and laboratory features may obscure the underlying mechanisms and complicate management.[7–9] In refractory ITP, immunosuppressive agents such as rituximab or other steroid-sparing therapies can be considered, although responses in pediatric patients remain variable.[6,7]

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Published pediatric reports of dual or overlapping thrombocytopenic disorders are very limited but highlight the frequent diagnostic delay without genetic evaluation and the necessity of tailoring treatment strategies to both immune and inherited components.[8,9] This underscores the urgency of comprehensive diagnostic approaches when clinical features do not align with typical ITP or BSS presentations.

In the present case, genetic testing revealed an *ETV6 c.115C>T (p.Arg39*)* variant associated with thrombocytopenia and leukemic predisposition, and a *GP1BB c.338A>T (p.Tyr113Phe)* variant diagnostic of BSS, underscoring the critical role of comprehensive molecular analysis.

The key clinical question addressed by this report is how to achieve an accurate diagnosis and safely manage overlapping inherited (BSS) and acquired (ITP) thrombocytopenias in a pediatric patient carrying a leukemogenic *ETV6* variant—thereby guiding therapeutic decisions and informing long-term surveillance strategies. The purpose of this case report is to demonstrate these diagnostic and management challenges, while providing insights into tailored treatment strategies and follow-up in such rare overlapping conditions.

Case Presentation

An 8-year-old girl presented with recurrent epistaxis beginning at age 3, which intensified by age 5. She experienced mucosal bleeding, bruising, and thrombocytopenia. No hematuria was reported. At age 6, she required multiple cauterizations for severe epistaxis and was hospitalized. She responded well to IVIG and was discharged in stable condition. A year later, a post-traumatic iliac fossa hematoma was managed with prednisolone, though platelet counts dropped during steroid tapering.

Bone marrow biopsy demonstrated variable cellularity without evidence of malignant infiltration. A rapid heme panel (RHP) identified a germline ETV6 mutation [c.115C>T, p.(Arg39*)], indicating thrombocytopenia and an increased risk of acute myelogenous leukemia (AML). Additionally, a GP1B-beta (GP1BB) variant [c.338A>T, p.(Tyr113Phe)] leading to a missense mutation was detected. A review of her platelet morphology revealed size variability, including large and giant platelets, a feature likely associated with the heterozygous GP1BB mutation.

Since diagnosis, platelet counts ranged from 35–170 $\times 10^9$/L, with a nadir of 18 $\times 10^9$/L in September 2023 requiring IVIG. She initially received IVIG in December 2020, followed by prednisolone from March to August 2021 with good response. Eltrombopag was given for six months but discontinued in June 2022 due to leukemic risk. Thereafter, platelet counts stabilized at 50–170 $\times 10^9$/L without major bleeding, with intermittent IVIG, antifibrinolytics, and local measures used for counts <30 $\times 10^9$/L or active bleeding. Table 1 shows a summary of genetic findings.

Table 1 Genetic Findings Summary

Gene	Transcript	Variant (cDNA/ Protein)	Genotype	Consequence	Inheritance	Classification	Associated Phenotype
ETV6	NM_001987.5	c.115C>T, p.(Arg39*)	Heterozygous	Stop gained	AD	Likely pathogenic	Thrombocytopenia 5
GP1BB	NM_000407.5	c.338A>T, p.(Tyr113Phe)	Heterozygous	Missense variant	AD/AR	Variant of uncertain significance (VUS)	Platelet disorder
NBEAL2	NM_015175.3	c.6919+4G>T (intronic)	Heterozygous	Splice region variant	AR	Variant of uncertain significance (VUS)	Gray platelet syndrome (unlikely, AR inheritance)
SOS1	NM_005633.3	c.3251G>A, p.(Arg1084Lys)	Heterozygous	Missense variant	AD	Variant of uncertain significance (VUS)	Noonan syndrome (not consistent with phenotype)

While the ETV6 mutation increases the risk of hematologic malignancy, the presence of the GP1BB mutation may exacerbate bleeding beyond what is typically observed in ETV6-associated cases, suggesting a potential disease-modifying gene and indicating a variant of uncertain significance (VUS). These findings confirmed a diagnosis of Bernard-Soulier syndrome in conjunction with immune thrombocytopenia.

Family screening revealed that the patient's 4-year-old brother carried the GP1BB mutation without the ETV6 variant, supporting the diagnosis of inherited BSS and identifying the ETV6 mutation as a de novo or maternally/paternally inherited pathogenic variant.

Therapeutic management included administration of two doses of IVIG to address low platelet counts associated with thrombocytopenia. Eltrombopag was discontinued due to its potential risk of promoting progression from myelodysplastic syndromes (MDS) to AML.

The patient received two IVIG doses and corticosteroids. Due to the ETV6 mutation and leukemic risk, eltrombopag was discontinued. Aminocaproic acid (Amicar) was administered for acute bleeding episodes. Long-term management includes annual monitoring of platelet count, bone marrow morphology, and surveillance for hematologic malignancy by a geneticist.

Discussion

ITP is an acquired autoimmune disorder characterized by a low platelet count despite a normal bone marrow profile.[1] It is also known as idiopathic thrombocytopenic purpura.[3,4] The disorder primarily affects primary hemostasis, leading to a prolonged bleeding time.[2] Clinically, ITP most often presents with mucocutaneous bleeding manifestations such as purpura, epistaxis, ecchymoses, menorrhagia, and hematuria, although some patients may remain asymptomatic.[6,7]

ITP involves antibody-mediated destruction of circulating platelets and impaired platelet production, resulting in thrombocytopenia. Typically, IgG-type autoantibodies target platelet glycoproteins IIb/IIIa, disrupting platelet aggregation. The presence of these autoantibodies promotes opsonization and subsequent phagocytosis of platelets by splenic macrophages. Additionally, they may also impair megakaryocytes, the cells responsible for platelet production.[3–5] Despite these disruptions, the morphology of circulating platelets typically remains normal.[6]

Management of ITP depends largely on disease severity. Mild cases may only require close observation, while severe cases necessitate platelet transfusion, intravenous immunoglobulins (IVIG), or corticosteroids.[6]

Medications for chronic ITP with relapses include a chimeric monoclonal antibody targeting CD20-positive B cells (rituximab) and romiplostim, a thrombopoietin receptor agonist that stimulates platelet production.[2] Rituximab has been systematically studied in children, showing overall response rates of up to 68%, though durability is variable.[10,11] If these therapies fail and relapses persist especially during corticosteroid tapering, splenectomy may be considered as a definitive treatment option.[6,9]

BSS is an inherited platelet disorder characterized by macrothrombocytopenia, characterized by abnormally large and reduced number of platelets and defective platelet adhesion. The condition results from mutations affecting the GPIb-IX-V complex, a critical receptor for von Willebrand factor that mediates platelet tethering to the subendothelium at sites of vascular injury.[7] Dysfunction or absence of this receptor impairs the initial steps of primary hemostasis, leading to prolonged bleeding times and a heightened risk of severe mucocutaneous bleeding episodes.

Management of BSS primarily involves supportive care, including the use of antifibrinolytic agents during minor bleeding episodes and platelet transfusions in cases of significant hemorrhage or before surgical procedures. Recombinant activated factor VII (rFVIIa) has also been reported as a hemostatic option in selected cases.[12]

This case demonstrates the complexity of diagnosing overlapping inherited and acquired thrombocytopenias. The coexistence of ITP and BSS complicated the clinical presentation and therapeutic options. Our patient responded to IVIG and corticosteroids, but eltrombopag was discontinued because of the germline ETV6 variant. Literature indicates that thrombopoietin receptor agonists such as eltrombopag can increase the risk of leukemic transformation in patients with predisposition syndromes.[13–15]

Genetic testing played a pivotal role in clarifying the diagnosis, informing treatment decisions, and guiding family screening. It highlights the need for comprehensive evaluation in children with persistent or atypical thrombocytopenia.

Published pediatric cases describing the coexistence of ITP and inherited platelet disorders are extremely rare, and to our knowledge, no prior pediatric report has combined ITP, BSS, and an ETV6 variant.[8,9]

This report has several limitations. First, follow-up duration is limited, precluding definitive conclusions regarding long-term outcomes and leukemic risk. Second, functional platelet studies (aggregation/adhesion assays) were not performed and could have provided additional mechanistic insight. Third, unrecognized genetic or environmental modifiers may have influenced the phenotype despite current testing. These factors should be considered when interpreting our findings.

In summary, this case supports early, comprehensive genetic testing in children with persistent or atypical thrombocytopenia to avoid misclassification, guide therapy (including cautious use of immunosuppressants and avoidance of TPO-R agonists in predisposed patients), and tailor surveillance. Future work—including multicenter registries of overlapping acquired/inherited thrombocytopenias—could clarify prevalence, refine diagnostic algorithms, and inform long-term monitoring strategies.

Conclusion

This rare case of coexisting ITP and BSS in a pediatric patient, further complicated by a germline *ETV6* variant, underscores the importance of integrating clinical assessment with comprehensive genetic testing. Accurate diagnosis and risk stratification are essential for safe and effective management, particularly as mutations such as *ETV6* directly alter therapeutic choices—most notably by discouraging the use of thrombopoietin receptor agonists due to leukemic risk.

Beyond its novelty, this case highlights how inherited and acquired thrombocytopenias may coexist and interact in children, providing valuable insights for clinical decision-making. It supports the incorporation of genetic testing into future pediatric thrombocytopenia guidelines, especially in atypical or treatment-refractory cases. Finally, it highlights a research priority to explore how predisposition genes like *ETV6* influence outcomes and to build evidence for long-term surveillance strategies in such complex scenarios.

Ethical Approval

Formal ethical committee approval was not required for this case report as per institutional policy.

Informed Consent

Written informed consent was obtained from legal guardians for the publication of any potentially identifiable images or data included in this article.

Author Contributions

All authors made a significant contribution to the work reported, whether that is in the conception, study design, execution, acquisition of data, analysis and interpretation, or in all these areas; took part in drafting, revising or critically reviewing the article; gave final approval of the version to be published; have agreed on the journal to which the article has been submitted; and agree to be accountable for all aspects of the work.

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Disclosure

The authors declare no conflicts of interest in this work.

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