

A Rare Case report on Bernard soulier syndrome

ABSTRACT

Our aim in this case report is to present the case of a fifteen-year-old boy diagnosed with Bounard soulier syndrome [BSS], to evaluate how the disease was managed, and to identify any shortcomings in its treatment. The patient previously diagnosed with BSS presented with epistaxis and vomiting episodes associated with blood. Immediate Complete blood picture was ordered and tranexemic acid was administered suspecting bleeding in the esophageal/gastric lining. The reports showed thrombocytopenia [$27,000 \text{ } 10^9/\text{L}$] with large sized platelets, after which Random donor platelets was administered along with antithrombolytics and vitamin supplements. Patients with BSS often experience variable frequency of bleeding manifestations due to fluctuating platelet levels and prompt management to rise platelet levels is considered important to for better patient outcome and quality of life. Females with BSS may be more prone to heavy bleeding in their menstrual period. Patient and parent [for pediatric patients] counselling help them understand this condition requiring life time interventions and monitoring. Helping them understand about possible risk of bleeding with other meds such as anticoagulants and advising to refrain from it may help. Constant supervising, reassuring and prompt medical intervention will contribute to positive patient outcomes.

Keywords: Bernard soulier syndrome, Giant platelets, pediatrics, Random donor platelet, GPIb-V-IX complex mutation

1. INTRODUCTION

Bernard Soulier syndrome (BSS) is a rare inherited platelet disorder with a prevalence of one in a million people [1]. It is caused by genetic abnormalities in the function of the GPIb-V-IX complex, which is required to bind von-Willebrand factor IX [2]. The defective GPIb-V-IX complements cannot attach to the endothelium, leading to adhesion failure, and increased patient bleeding tendencies. Mutations in four genes (i.e., GPIb α , GPIb β , GPIX, and GPV) are mainly responsible for creating the products that combine to form the defective complex [3]. These mutations have been documented as missense, frameshift, or deletions [4]. The clinical signs of BSS involve mucocutaneous bleeding, with the most common presentations being unconstrained bruising, gum bleeding, & epistaxis. In addition to the typical clinical signs, the disorder can also present with menorrhagia, gastrointestinal bleeding, & profuse bleeding after surgery or injury that may be troublesome to control [5]. These clinical signs of BSS and the associated thrombocytopenia are more likely to be noted in early childhood. Still, it is often misdiagnosed as other bleeding disorders, such as immune thrombocytopenia (ITP) [6]. Due to the rare presentation of BSS and its similar symptomatology to other bleeding disorders, cases can often go undiagnosed or misdiagnosed. In developing countries, where healthcare resources are limited, diagnosing BSS correctly and utilizing resources for appropriate treatment is paramount [7].

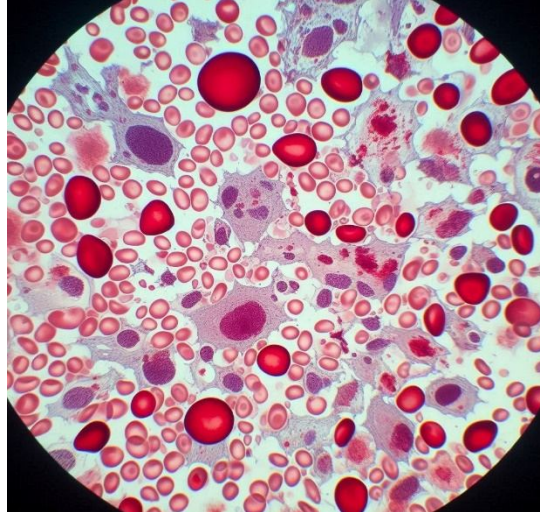


Fig 1: Uneven and giant platelets on blood smear

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2. CASE PRESENTATION

A 15 yr. Old boy admitted in the hospital with the chief complaints of epistaxis~100ml and 2 episodes of vomiting characterized by dark brown coloured vomitus. The platelet count was $9,000/\text{mm}^3$ (Outside investigational report) and was initially given with Injection Tranexamic acid 500mg twice a day and 1 pint of Ringer lactate. Upon general examination, the patient looked pale; alert, oriented and cooperative with normal vital signs. On systemic examination the findings were unremarkable. Emergency Complete blood picture showed that the patient was anemic and the platelet count was decreased to $27,000 \text{ } 10^9/\text{L}$ marked by giant platelets, a hemoglobin of 8mg/dL, WBC count of $6.13 \text{ } 10^9/\text{L}$, Mean corpuscular volume of 25.3fL, Mean corpuscular hemoglobin of 66.4pg, Mean corpuscular hemoglobin concentration of 31.6g/dL was found. The patient has been diagnosed as Bernard- Soulier Syndrome at the age of 9 years. He had similar complaints 6 months back for which no medical intervention was required. History of cough on & off is informed. Treatment started with Inj. tranexamic acid 500mg BD, Inj. ondansetron 4mg BD, & 4 pint RDP (Random donor platelet) transfusion. On the next day status post 4 pint of RDP transfusion, epistaxis subsided and the patient received Factor VII 5000U/ IV in 100ml normal saline, Injection Tranexamic acid 500mg BD & 1 pint of PC (Platelet concentrate) transfusion. On the next day of admission Epistaxis subsided and the patient was prescribed with Inj. tranexamic acid 500mg BD, Tab. Iron folic acid [IFA] 325mg OD & Tab. Vitamin C 500mg OD. Complete blood picture report of patient shows a hemoglobin of 6g/dL, RBC of $2.78 \text{ } 10^{12}/\text{L}$, WBC of $8.55 \text{ } 10^9/\text{L}$ and platelet of $9000 \text{ } 10^9/\text{L}$. Regards of these findings, 4 pint of RDP transfusion was again planned and was transfused the next day with post transfusion prescription of Inj. Tranexamic acid 500mg BD, Tab. IFA 325mg OD & Tab. Vitamin C 500mg OD. No active bleed has been observed and immediate CBP of the patient was advised by the doctor. The reports reveals slight increase in platelets to $16,000 \text{ } 10^9/\text{L}$. 2 pints of RDP was again planned after which the blood picture investigation shows increasing platelets to $21,000 \text{ } 10^9/\text{L}$ & Hemoglobin 8g/dL. The treatment was continued with Inj. tranexamic acid & vitamin supplements along with transfusions with a goal to stabilize the platelet count in the patient. The patient was mild anemic & in good health with follow up prescription of Iron folic acid.

Table 1. Laboratory findings of the patient

Parameters	Day 1	Day 2	Day 4	Day 7
Hb (g/dL)	8	6	7	8
WBC ($10^9/L$)	6.13	8.55	8.52	8.55
RBC ($10^{12}/L$)	-	2.78	2.85	2.92
PLT ($10^9/L$)	27,000	9000	16,000	21,000

71 **Note:** WBC- White blood cells (4-11 $10^9/L$), RBC- Red blood cells (3.50-5.50 $10^{12}/L$), Hg-
72 Hemoglobin (12-13 mg/dl), PLT- Platelet count (150-450 $10^9/L$)

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3. DISCUSSION

76 The uncommon hereditary bleeding illness known as Bernard-Soulier syndrome, or
77 hemorrhagic thrombocytopenic dystrophy, was initially reported by Bernard and Soulier in
78 1948 and affects the megakaryocyte cell line. The condition is caused by a quantitative or
79 qualitative deficiency in the platelet membrane glycoprotein Ib/IX/V complex, which is a
80 receptor for von Willebrand factor. Less than one in a million cases were documented, and it
81 appears to be more common in nations with high rates of consanguineous marriage. Its test
82 results show extended bleeding time, giant platelets, and thrombocytopenia. BSS is
83 characterized by a constellation of mild hemorrhagic manifestations, including easy bruising,
84 epistaxis, gingival bleeding, and excessive menstrual bleeding. Symptoms typically start in
85 childhood but diagnosis may be delayed until late adulthood due to subtle bleeding. Bleeding
86 severity and frequency can fluctuate, often decreasing with age. However, females with BSS
87 may still have heavy periods and bleeding issues during childbirth [8].

88
89 The GPIb-IX-V complex plays a vital role in processes like inflammation, hemostasis, and
90 thrombosis. GP1ba, the linchpin of this complex acts as the principal ligand-binding domain,
91 interacting with factors crucial for these processes. Mutations, particularly within the GP1BA
92 gene, disrupt the function or expression of GP1ba, leading to Bernard-Soulier syndrome.
93 BSS can manifest due to a spectrum of mutations in the GP1BA gene, including missense,
94 nonsense, frameshift mutations, and insertions/deletions. A study by Ozdemir et al.
95 described a pediatric BSS case initially misdiagnosed as neonatal immune
96 thrombocytopenia due to severe thrombocytopenia. This patient exhibited normal GPIX
97 (CD42a) expression, harbouring a homozygous nonsense mutation in the GP1BA gene [9].
98 Ghalloussi et al. documented the inaugural instance of BSS attributable solely to a complete
99 deletion of the GP9 gene [10]. Minkov et al. identified two novel mutations within genes
100 encoding key components of the GPIb-IX-V complex [*GP1BA* & *GP9* genes], potentially
101 leading to Bernard-Soulier syndrome. One mutation in the GP9 gene results in an amino acid
102 substitution (p.Cys38Arg), while the other, a nonsense mutation in the GP1BA gene,
103 introduces a premature stop codon (p.Gln346Ter). This latter mutation likely truncates the
104 GP1ba protein, potentially rendering it dysfunctional and contributing to BSS pathogenesis.
105 A triad of low platelet count, macro thrombocytopenia, and diminished or absent expression
106 of GPIb-IX-V complex components constitutes a definitive diagnostic indicator for BSS [11].
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108 Flow cytometry aids in diagnosing hereditary platelet disorders, particularly in pediatric
109 cases, yet confirms only 60% of diagnoses, necessitating further platelet morphology and
110 laboratory analyses for a comprehensive diagnosis of Bernard-Soulier syndrome. BSS is
111 further characterized by a diminished response to ristocetin in light transmission platelet
112 aggregometry. Clinical and laboratory evaluations reveal distinct variations among patients
113 with Bernard-Soulier syndrome. While some GP1ba mutations are phenotypically silent,
114 others manifest as a spectrum of BSS severity. This phenotypic heterogeneity is attributed to
115 structural alterations within the receptor itself[9].
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117 Lentiviral gene editing holds promise for treating severe inherited bleeding disorders like
118 Bernard-Soulier syndrome, concerns remain regarding its potential to induce oncogenic or
119 infectious changes, along with other unforeseen transformations in targeted cells.
120 Conversely, Adeno-associated virus (AAV)-based gene therapy offers a potentially safer
121 approach due to its epigenetic nature. The expression of transgenic proteins introduced by
122 AAV therapy tends to diminish over time. Future research aimed at minimizing risk factors
123 associated with lentiviral vectors could pave the way for a definitive and efficient cure for
124 BSS by enabling single-cell line correction[12]. In our case, patient epistaxis has been not
125 resolved alone by tranexamic acid and needed severe RDP transfusions to subside
126 bleeding.
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128 **4. CONCLUSION**

129 Accurate and prompt diagnosis of Bernard-Soulier syndrome is paramount for effective
130 disease management. Given its clinical overlap with other platelet disorders, meticulous
131 differential diagnosis is essential. Platelet transfusion should be approached cautiously.
132 Empowering patients through comprehensive education regarding BSS and its potential
133 complications is crucial; this fosters self-care strategies that enhance patient well-being.

134 **AUTHORS' CONTRIBUTIONS**

135 Every author have contributed their part in all the aspect of this manuscript. All authors read
136 and approved the final manuscript.
137

138 **DISCLAIMER (ARTIFICIAL INTELLIGENCE)**

139 Author(s) hereby declare that generative AI technologies such as Large Language Models
140 have been for Text to image generation in the manuscripts.

141 Details of the AI usage are given below:

142 1. Version name: COPILOT on Windows 11

143 2. Prompt: Create me a simplest and realistic image a slide under microscope of how giant
144 platelet cells along with RBC, WBC will look on a slide under microscope in bernard soulier
145 patient.

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196 **ABBREVIATIONS**

197 BSS- Bernard Soulier syndrome

198 RDP -Random donor platelet
199 AVV-

Adeno-associated

virus