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Bernard Soulier Syndrome misdiagnosed as Von Willebrand Disease

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Abstract

Bernard–Soulier syndrome (BSS) is a hereditary bleeding disorder of platelet adhesion caused by defects in the glycoprotein (GP)Ib/IX/V complex. This complex is found on the surface of platelets and plays a vital role in blood clotting. A diagnosis is made by a combination of coagulation tests, flow cytometry, and aggregometry studies. We present a case of a 21-year-old patient who presented with bleeding from the nose, abdominal pain, and heavy menstrual bleeding. Patients have also reported a history of recurrent episodes of nasal and gum bleeding since childhood. On examination, the patient had pallor. Investigations show microcytic hypochromic anemia with anisopoikilocytosis, moderate thrombocytopenia, many giant cells & few small clumps seen on the smear. Flow cytometry shows the absence of CD42b and decreased ristocetin-induced platelet aggregometry. A diagnosis of Bernard-Soulier Syndrome was made. She was advised not to use any drugs inhibiting platelet function, and symptoms are medically managed. She was discharged by taking all necessary precautions.

Introduction

BSS is an inherited disease characterized by macrothrombocytopenia and impaired platelet function. Recent estimates suggest that Bernard Soulier syndrome affects 1 in a million people. More than 200 cases have been reported worldwide [1]. It is caused by a receptor defect in the GPIb-IX-V complex that is necessary for binding to von Willebrand factor [2], [3]. These

patients typically present with epistaxis, petechial, or gingival bleeding with onset in infancy. Other symptoms include genitourinary or gastrointestinal bleeding and menorrhagia. Trauma or surgery, especially in mucosal regions, may also lead to excessive bleeding.

To form the GPIb-IX-V complex, the products of four genes (GP1BA, GP1BB, GP9, and GP5) assemble within maturing megakaryocytes in the bone marrow [4]. Different mutations (deletions, insertions, and nonsense mutations) in GP1BA, GP1BB, or GP9 cause BSS and are distributed over these entire genes [1], [2], [5]. Most of these mutations prevent the formation or trafficking of the complex through the endoplasmic reticulum and Golgi apparatus and alter receptor expression [6], [7], [8]. Most cases of BSS are inherited as an autosomal recessive genetic trait [9].

Case Presentation

A 21-year-old female, a single child of a consanguineous marriage, presented with nosebleeds, abdominal pain, and heavy menstrual bleeding. Nosebleeds started 24 hours back and stopped temporarily after applying pressure. Abdominal pain is intermittent, cramping quality, and has been present for three days. The menstrual cycle started seven days back; she used 3 to 4 pads every day and noticed clots in most of them. The patient has a history of multiple episodes of ecchymosis, nasal and gum bleeding since two years of age, but a definitive diagnosis has not been made till now. She is on OCPs. On examination, the patient had pallor. There is no icterus, cyanosis, clubbing, or lymphadenopathy. Vitals are stable. Gastrointestinal system examination revealed mild abdominal discomfort. Other systemic examinations are unremarkable.

Investigations at the time of admission showed hemoglobin of 6.2 mg/dL (reference range {N}: 12-16 mg/dL), platelet count of 90000/ cu mm (N: 1.5-4 105/cu mm), TLC 5.27/mm^3 (N:4500-11000 /mm3), MCV 59 fl (N:75-95 fl) and, MCHC 27g/dl (N:31- 36 g/dl). Serum iron studies also showed iron deficiency. Peripheral blood smear findings are as follows: RBCs are predominantly microcytic hypochromic; some normocytes, pencil forms, and teardrop cells are also seen; WBC total and differential counts are within normal limits; many giant platelets [Figure 2] and few small clumps seen on the smear with moderate thrombocytopenia [Figure 1]. Her previous smears were also similar to this one. She has previously received one unit of platelet transfusion and two units of packed RBCs. At that point, PT was 17.6 seconds (N: 11-15 sec), INR-1.34 (N: 1.0), and the sickling test was negative.

For further evaluation, the patient was advised a bleeding profile in which PT, aPTT, and factor XIII were all normal. Then, for further evaluation, the patient was advised on platelet aggregometry and flow cytometry. Her platelet aggregometry test revealed absent aggregate in response to restocetin, even with adding plasma. Flow cytometry showed the absence of CD42b (GP1B α), suggesting BSS. She was prescribed tranexamic acid for current menorrhagia, iron supplements for anemia, and advised to continue OCPs. The patient was advised to avoid platelet transfusions unless the platelet count is less than 10,000. Transfusions are also indicated in case of bleeding manifestations to prevent infections and if she has to take drugs that inhibit platelet function.

Figure 1: Peripheral Blood smear showing thrombocytopenia, microcytic anemia

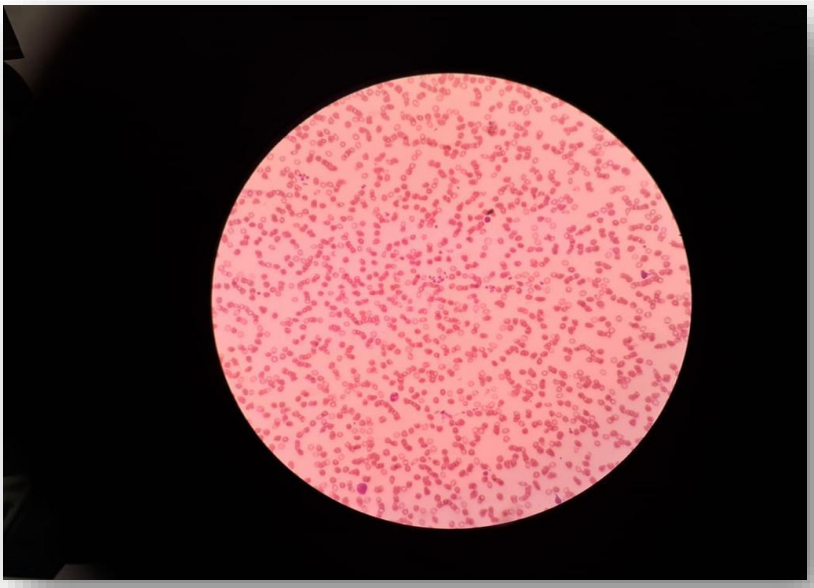
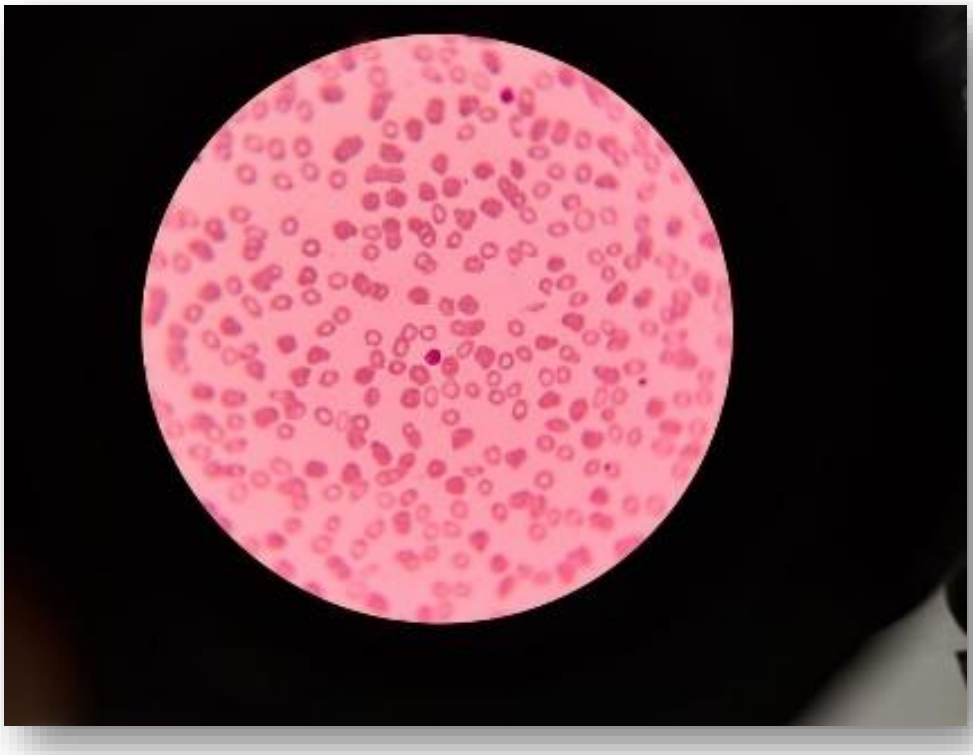


Figure 2: Peripheral Blood smear showing megakaryocytes



Discussion

BSS is a rare inherited platelet dysfunctional disorder characterized by giant platelets and bleeding episodes manifesting as clinical symptoms such as epistaxis, menorrhagia, and easy bruising [10].In 1948, Jean-Bernard and Jean-Pierre Soulier described the first male patient who presented with repeated episodes of bleeding throughout his life and eventually died at the age of 28 years from an intracranial hemorrhage sustained after a bar fight [1][11]. It is caused by genetic abnormalities in the function of the GPIb-V-IX complex, which is required to bind von Willebrand factor IX [12] .BSS is inherited via autosomal genes. Hence, it is prevalent in male and female patients [11][13].

Since its discovery, there have been significant advancements in understanding the molecular pathogenesis of disease. The symptoms are due to thrombocytopenia, abnormal platelet coagulation activity, and abnormal interactions with VWF, thrombin, P-selectin, and αMβ2.

The median age of presentation ranges from 5 to 25 years old, with our patient being 21 years old. This patient had a platelet count of 90,000 at the time of presentation. The cause of thrombocytopenia was uncertain at that point, and initially, they suspected it to be Von Willebrand Disease (vWD). Although flow cytometry did confirm the diagnosis of BSS, the initial investigations are similar to other platelet disorders like vWD and Immune thrombocytopenic purpura (ITP). Platelet aggregation studies (i.e., light transmission aggregometry) showing decreased or absent response to ristocetin indicate BSS, further confirmed by flow cytometry depicting the low expression of Glycoprotein Ib.[14] Similarly, diagnosis is confirmed in this case after doing a ristocetin-induced platelet aggregation test and flow cytometry in 2023. In BSS, there is decreased or absent GP1B, resulting in impaired platelet aggregation with ristocetin, whereas, in vWD, strong platelet aggregation occurs in response to the addition of plasma [14].

In this case, flow cytometry revealed the absence of CD42b, suggesting a mutation in GP1B alpha, which resulted in a defect in the GP1B/IX/V complex. Even though her first visit to the hospital was at the age of 9 years, lack of awareness among parents, low socioeconomic status, and irregular follow-ups have caused a delay in the diagnosis.

BSS is more likely to be seen in consanguineous marriages due to its autosomal recessive inheritance. Consanguineous marriages are more common in Southeast Asian countries like India, Pakistan, and China. In contrast, in the case of ITP, an acquired disease, the presence of a family history of ITP can confirm its diagnosis [15]. Therefore, proper counseling should be done for these families antenatally. Mothers with BSS may develop severe hemorrhages and should be monitored throughout pregnancy and postpartum for any bleeding symptoms. If recombinant factor VII has been given, thrombo-prophylaxis should be considered individually [16].

The primary treatment for BSS is supportive care, including using anti-fibrinolytic agents for mucosal bleeding and avoiding antiplatelet food and drugs. Desmopressin and recombinant factor VIIa may also be helpful in some cases. Platelet transfusion is avoided unless necessary because patients develop antibodies to missing glycoproteins that can compromise the effect of

future transfusions. We prescribed tranexamic acid for any future episodes and advised her to avoid using drugs that promote platelet aggregation.

Conclusion

BSS can be identified by bleeding manifestations from childhood, thrombocytopenia, and Ristocetin-induced platelet aggregometry. Doctors need to be cautious when dealing with patients presenting with symptoms of a bleeding disorder, especially in areas where marriages between close relatives are common. Due to the rare presentation of BSS and its similar symptomatology to other bleeding disorders, cases are more likely to go undiagnosed. In developing countries, where healthcare resources are limited, early and accurate diagnosis is crucial to prevent further complications like severe bleeding diathesis.

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