Case Report

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Bernard–Soulier syndrome (BSS) with uncontrollable menorrhagia

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Abstract:

Menorrhagia is a common problem in women of reproductive age group and 5% of women between 30 and 49 years of age group consult their general practitioner for this problem. Menorrhagia occurring in adolescent age group and perimenopausal age group is chiefly due to anovulatory cycles. In perimenopausal age group, local pathology like leiomyomas can also contribute to menorrhagia. Recently, bleeding disorders like von Willebrand Disease, single coagulation factor deficiencies particularly factor XI, VIII, Factor V and platelet function disorders have been found to be prevalent in patients presenting with menorrhagia. Bernerd soulier syndrome is extremely rare haemostatic disorder due deficiency in GP IB/IX/V receptor complex present on platelet membrane which is necessary for platelet aggregation. As a result of the defect patients have prolonged bleeding time, which might vary in symptoms ranging from spontaneous self- limiting epistaxis to life threatening haemorrhage. Here we report a case of 31-year-old woman known case of Bernard soulier syndrome with severe menorrhagia treated with mirena insertion and course of complication and its management.

Keywords:

Bernard–Soulier syndrome, coagulopathy, menorrhagia

Introduction

The aetiology of menorrhaegia can be local or systemic disorders but a specific cause is identified in less than 50% of the cases and in remaining cases dysfunctional uterine bleeding is diagnosed.[1] Bernard–Soulier syndrome (BSS) was first recognized by Jean–Bernard and Jean–Pierre Soulier in 1948 in a young male patient who has prolonged bleeding time, mild-to-moderate thrombocytopenia, and very large platelets.[2] This syndrome is extremely rare, and only 100 cases have been reported, mostly in the populations of Japan, Europe, and North America. Prevalence has been estimated at <1/1,000,000.[3] In India, the reported cases are 27 till date.[4] The mode of inheritance is usually autosomal recessive with autosomal dominant pattern seen in isolated case.

The disorder is caused by a deficiency in glycoprotein (Gp) Ib/IX/V[5] a protein found on the surface of platelets. The GpIb-IX-V complex is composed of 4-transmembrane-polypeptide subunits, disulfide-linked alpha and beta subunits of the GpIb, and noncovalently associated subunits GpIX and GPV.[6] The gene of each of the subunits has been cloned and their chromosomal locations are identified as follows: GpIb-alpha gene (chromosome-17), GpIb-beta gene (22q11.2), GpIX gene (3q21), and GpVgene (3q29). This protein is essential for aggregation of platelets around injured blood vessels through a receptor to the von Willebrand factor. BSS can occur due to defect in any of the subunits of the GpIb/IX/V complex. Majority of cases are due to defect in the GpIb-alpha subunit, either qualitative or quantitative. Identifying isolated defective ristocetin-induced agglutination when placed in an aggregometer makes the definitive diagnosis of BSS. The diagnosis may be confirmed biochemically or by genotyping.

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Case Report

A 31-year-old nulliparous female, a known case of BSS diagnosed at the age of 15 years, attended outpatient department (OPD) of Medical College, Kolkata on November 4, 2017, with complaints of severe bleeding per vagina for last 7 days. She had a removal and reinsertion of new levonorgestrel intrauterine system (LNG-IUS) 7 days back at Medical College, Kolkata. Since then, she started bleeding off and on and turned heavy.

Past History

She had long-standing history of epistaxis, gum bleeding, and passage of clotted blood with stool for 6 months of age for which she did not receive any definitive treatment. She attained menarche at 10 years with passage of large clots and had to take tranexamic acid and progestogens to stop bleeding. She developed severe anemia by 11 years and was hospitalized several times for multiple units of blood transfusion. Detailed history did not reveal any family history of congenital bleeding disorder.

She had a diagnosis of ovarian cyst (7 cm × 7 cm) on pelvic ultrasound in 2001 at age 14. At that time, she was not diagnosed to be a case of BSS. The patient underwent left-sided ovariotomy and left-sided internal iliac ligation had to be done to control bleeding during laparotomy on April 21, 2001, in another Medical College of Kolkata. Histopathological report showed endometriotic cyst.

Postoperative investigation was done to identify the reason behind severe intraoperative hemorrhage. Blood investigation showed mild hemolytic anemia and a normal platelet count with mostly isolated large platelets. Platelet aggregation test was advised.

She visited the Institute of Immunohematology, ICMR, Mumbai, July 2002, and her blood investigations were as follows:

Platelet aggregation test revealed no aggregation of platelets in response to ristocetin and reduced aggregation in response to adenosine diphosphate (6 μg) and epinephrine (4 μg). Platelet count – 66,000/cmm, prothrombin time – 11.7 min (control 12.3 min), and APTT 31.3 min (control 32.3 min). Peripheral blood smear showed giant platelet with normal differential count. Platelet-associated immunoglobulin (by flow cytometry) was 15,000 abs/platelet (normal range: 1500–3200) (as the patient has history of blood transfusion). Patient's platelet showed highly reduced fluorescence with anti-Gp-Ib IX antibody and anti-Gp-Ib antibody (<40%) when compared with normal platelets, which showed normal fluorescence in response with these antibodies. Thus, the diagnosis was BSS. The patient was advised long-term iron therapy, low-dose COC, and oral tranexamic acid 2–4 days before menstruation starts. The patient was advised against unnecessary blood product transfusion and intake of nonsteroidal anti-inflammatory drug.

She had insertion of LNG-IUS on May 20, 2004, to control menorrhagia, but it got expelled after 15 days. The patient received 6 units of platelets transfusion again. The patient was regularly put on extended regimen (4 months) of oral contraceptive pill (OCP) to delay menstrual cycles and tranexamic acid.

The patient visited Medical College Hospital OPD for the first time on October 2012 with complaint of uncontrolled menorrhagia. She was treated with tablet ormeloxifene and gonadotrophin-releasing hormone (GnRH). After she became amenorrhoeic, LNG-IUS was inserted. Following that, the patient started to have regular menstrual cycles with scanty flow. She got married in 2014. Her quality of life improved.

On admission on November 4, 2017, she was clinically stable, but was markedly pale; her chest was clear and abdomen was soft with no organomegaly. Her blood investigation showed hemoglobin 6.9 g/dl, WBC 11300/cumm, and platelet 9000/cumm. Pelvic ultrasound was normal.

The patient was transfused 4 units of platelet and 3 units of PRBC. Tablet norethisterone (10 mg twice daily) and injectable antifibrinolytic agent and injection leuprolide (3.75 mg) were administered. The patient continued tablet ormeloxifene 60 mg twice weekly as prescribed with LNG-IUS reinsertion. After 48 h of conservative management, bleeding stopped and blood parameters were as follows: hemoglobin 9.1 g/dl, WBC 7300/cumm, and platelet 50,000/cumm.

The patient was discharged after 5 days in a stable condition with advice of oral iron therapy, oral tranexamic acid (500 mg) if necessary, tablet ormeloxifene (60 mg) twice weekly, and injection leuprolide after 28 days.

Follow-up

The patient never had any episode of menorrhagia till April 2018 and she continued follow-up till date. She used to get her platelet count checked at monthly interval and that dropped down to 20,000/cumm in February 2018; she never suffered from any episodes of menorrhagia.

Discussion

Menorrhagia is a common clinical problem and affects the quality of life in women who suffer. The most common cause of menorrhagia at adolescence is hormonal. Immaturity of hypothalamic–pituitary axis, resulting in anovulation is responsible for majority of

cases. Patients with inherited bleeding disorders can also present at puberty, with menorrhagia requiring immediate medical attention.

BSS is a rare hereditary bleeding disorder, characterized by prolonged bleeding time and thrombocytopenia with morphologically abnormal giant platelets. The platelet membrane is deficient in GpIb-V and GpI-IX, the primary defect being the absence of GpIb-receptor for Von-Willebrand factor. GpIb and GpIX exist as a heterodimer complex in the platelet membrane and constitute major receptor mediating platelet adhesion to endothelium of blood vessels. Bleeding time is excessively prolonged disproportionate to the degree of thrombocytopenia. Aggregation responses to adenosine-diphosphate, collagen, and adrenaline are normal. Typical finding in BSS is the absence of aggregation with ristocetin, which is not corrected by adding normal plasma or Von-Willebrand factor to the specimen.

Management depends on the severity of the condition. Patients require whole-blood/packed red cell/platelet transfusion in most cases. Repeated exposure to blood products raises risk for alloimmunization and platelet refractoriness. Factor-VIIa can also be used as alternative. However, factor VIIa may result in increased risk of thromboembolic events. Desmopressin, an antifibrinolytic agent, has been shown to shorten the bleeding time in some patients. Intractable bleeding at puberty in BSS patients has been treated with endometrial ablation, OCP and LNG-IUS, selective estrogen receptor modulator (SERM), and GnRH.

Pregnancy in BSS is associated with a variable course. Outcome varies among different patients, and even for the same patient in different pregnancies[3,5] it may be complicated by maternal and fetal morbidity of various severity.[2] Although the optimum mode of delivery is not clear, vaginal delivery is recommended unless obstetrically 3 indicated CS.

There is very high risk of life-threatening postpartum hemorrhage even after best possible care. Therefore, our patient was counseled against conception, although there are few case reports of successful pregnancy with BSS.

Conclusion

Hematological disorders should be taken under consideration before labeling the cause as idiopathic in cases of menorrhagia because a thin line saved our patient during her major surgical procedure before she was diagnosed to be a case of BSS. LNG-IUS insertion can be used as a procedure to control menorrhagia in this group of patients along with pretreatment with SERM, GnRH, and antifibrinolytic agent.

Declaration of patient consent

The authors certify that they have obtained all appropriate patient consent forms. In the form the patient(s) has/have given his/her/their consent for his/her/their images and other clinical information to be reported in the journal. The patients understand that their names and initials will not be published and due efforts will be made to conceal their identity, but anonymity cannot be guaranteed.

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Conflicts of interest

There are no conflicts of interest.

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