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Combined occurrence of Bernard-Soulier syndrome and prekallikrein deficiency

TO THE EDITOR: Bernard-Soulier Syndrome (BSS) and prekallikrein (PK) deficiency are two rare genetic disorders with autosomal recessive transmission patterns, and the combined occurrence of these two disorders is rare [1, 2]. In BSS, abnormalities are caused by glycoprotein (GP) Ib/IX/V complex defects, which constitute the Von Willebrand factor (VWF) receptor on the platelet surface [1, 3, 4]. This condition is clinically characterized by thrombocytopenia and prolonged bleeding time (BT) [5]. Common symptoms include easy bruising and gum and nose bleeding episodes [6].

Coagulation factor XII (FXII), PK, and high-molecular weight kininogen (HMWK) are the three important plasma proteins of the kallikrein-kinin system. Deficiencies in any of these factors are rare and diagnosed when the results of routine coagulation tests show a prolonged activated partial thromboplastin time (aPTT) [2]. Most cases of PK deficiency are asymptomatic. However, there had been a few reports on the association between severe PK deficiency and thrombotic phenomena and recurrent pregnancy losses [7].

In this report, we describe the first combined occurrence of BSS and PK deficiency in a 3-year-old girl who presented with recurring epistaxis.

A 3-year-old girl, who was born out of consanguineous marriage through caesarean section with a birth weight of 2,650 g and gestational age of 38 weeks, was admitted to our hospital with a history of recurrent nose bleeding and body bruising within a one-year duration. She was hospitalized numerous times due to similar complaints. No significant history of trauma, jaundice, fever, or previous blood transfusions was recorded. The mother had a history of anemia and thrombocytopenia during pregnancy with a platelet count of 90,000/μL and did not have any known disease before pregnancy. In addition, she had no history of medication use. Her past medical history was negative for any thromboembolic phenomena. No family history of similar illness was obtained.

The results of the patient's ENT (ear, nose, and throat) examination were not significant. She had active nose bleeding, and petechiae, purpura, and ecchymosis were observed in the limbs. Her systemic examination was essentially normal with no organomegaly.

Blood test results revealed a hemoglobin level of 12.2 g/dL and white blood cell count of 5,600/μL, with normal differential counts. Her platelet count was 37×10^3/μL and platelet morphology showed numerous giant platelets. Furthermore, the following laboratory tests were also obtained: BT (16 sec; control: 3–7 sec), prothrombin time (13.1 sec; control: 13.2 sec), aPTT (>180 sec; control: 34.1 sec), mixed PTT (35.3 sec), VWF (Ag=87%; VWF Ab=73%). The aggregating agent results were the following: ADP: 2 μmol/L; (63; normal, 50–150); ristocetin: 1.5 mg/mL (0; normal, 50–150); collagen: 2 μmol/L; (69; normal, 50–150); and arachidonic acid: 0.5 mmol/L (53; normal, 50–150). The result of the platelet aggregation test confirmed the diagnosis of BSS, a condition wherein platelets do not aggregate in response to ristocetin and is characterized by thrombocytopenia and giant platelets.

Factor VIII level was 62 mg/dL (normal, 60–150 mg/dL), factor IX level was 62 mg/dL (normal, 60–150 mg/dL), factor XI level was 72 mg/dL (normal, 50–110 mg/dL), and factor XII was 69 mg/dL (normal, 50–120 mg/dL). In addition, the absolute fibrinogen level was 2.4 mg/dL (normal, 1.5–4.5 mg/dL). The pre-incubation of plasma with the surface activator, kaolin, caused a rapid shortening of the abnormal

clotting time to normal values. Because of our experience, we evaluated the PK level with a clotting method using the Technoclone PK kit. The result showed a PK deficiency with a level of 1.3% (normal, >50%). HMWK level was 110% (normal, >50%).

The patient was treated with local hemostatic agents. Platelet concentrate was not given because the patient's nose bleeding stopped spontaneously. No episode of bleeding occurred after treatment.

Childhood epistaxis is a common complaint that usually decreases during adulthood; however, when frequent episodes are observed along with significant blood loss, it can be life-threatening [8]. Mucocutaneous hemorrhage is common in disorders of platelet function (including Von Willebrand disease and fibrinogenemia) [9].

Common inherited causes of platelet-related bleeding include BSS, Glanzmann thrombasthenia (GT), and gray platelet syndrome. So, it is important to evaluate platelet aggregation function in individuals suspected of having an abnormal platelet function. Aggregation test was performed with Light Transmission Aggregometry (LTA) in our case.

BSS is clinically characterized by giant platelets, thrombocytopenia, and a prolonged BT [10]. Our patient was thrombocytopenic with prolonged BT and giant platelets. Easy bruising and bleeding episodes involving the gums and nose are typical symptoms of BSS [6]. Severe and life-threatening bleeding episodes are rare and may occur with surgery or after major trauma. Nasal bleeding and body bruising with no history of trauma were observed in our patient. However, bleeding was not severe and it stopped spontaneously.

PK, or Fletcher factor, plays a role in the early phase of blood coagulation that modulates the activation of clotting factors XI and XII [11]. However, according to some studies, a proteolytic pathway independent of FXII exists, which is associated with PK activation [12]. The incidence of consanguinity has been shown to be increased in PK deficiency (Fletcher trait) cases [13]. Our patient was born out of consanguineous marriage. PK levels ranged from 0% to 30% in most cases [14]. The PK level of our patient was within this range (1.3%).

A severely prolonged aPTT along with an increased preincubation time, which is a characteristic of PK deficiency, was normalized due to FXII autoactivation. Thus, the deficiency is diagnosed when PTT is prolonged with no other explanation and no clinical history of bleeding disorders. Although most cases are asymptomatic, few reports are associated with PK deficiency with a possible procoagulant tendency and loss of pregnancy [15]. In the recent case, PTT was prolonged with no history of bleeding disorder.

According to some studies, PK deficiency is associated with FXII deficiency and Von Willebrand disease [11]. However, test results for these disorders were negative in our patient. Moreover, the liver function tests were normal in our patient, which excluded a decreased synthetic liver function caused by low serum PK level.

Nasal bleeding in our patient could potentially be explained by other factor deficiencies that might have tilted the hemostatic balance toward anticoagulation. However, the low levels of PK activity confirm the diagnosis of PK deficiency. Spontaneous bleeding seems to be extremely rare in PK deficiency and may reflect an underreported state secondary to the rarity of the condition. Constantin *et al*. [11] reported moderate bleeding tendencies in individuals with PK deficiency. Our patient had several episodes of bleeding.

Our case was a combined occurrence of BSS and PKK deficiency. Therefore, the main cause of bleeding in this case was difficult to determine. However, because of the rarity of bleeding due to PK deficiency and recurring nose bleeding and body bruising, BSS was likely the primary cause of bleeding in this patient.

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A case of adult-onset Still's disease accompanied by pseudo-gray platelet syndrome

TO THE EDITOR: A 39-year-old man with a 1-week history of fever, polyarthralgia, sore throat, and a salmon pink rash was admitted to our hospital. Laboratory findings based on blood samples, which were collected with ethylenediaminetetraacetic acid (EDTA) and counted 30 min after venipuncture, were as follows: white blood cell (WBC) count, 38,840/μL (neutrophils, 94.0%; eosinophils, 1.0%; monocytes, 1.0%; lymphocytes, 1.0%; basophils, 0.8%; metamyelocytes, 2.2%); red blood cell (RBC) count, 4.19×10^6/μL; hemoglobin level, 12.1 g/dL; platelet count, 138×10^3/μL; immunoglobulin (Ig)G, 1.050 g/dL; IgM, 0.184 g/dL; IgA, 0.264 g/dL; and C-reactive protein, 25.3 mg/dL. The antinuclear antibody titer was 1:40. The ferritin level was 953.5 ng/mL (normal range, 5–157 ng/mL). Finally, the patient was diagnosed with adult-onset Still's disease (AOSD). On day 5 after admission, the patient was treated with prednisolone (PSL, 40 mg/day) and subsequently with PSL in combination with tacrolimus (TAC, 2 mg/day). On the day after admission, the platelet count in EDTA-anticoagulated blood samples examined at 60–120 min after venipuncture remained low ($21–87\times10^3$/μL). On day 11 after admission, the platelet count in EDTA- and heparin-anticoagulated blood samples examined at 120 min after venipuncture was 33×10^3/μL and 320×10^3/μL, respectively. The EDTA blood film showed gray, aggregated agranular platelets, whereas the heparin blood film showed normal platelets. On day 14 after admission, complete blood counts were obtained in blood samples collected with EDTA, sodium citrate, and heparin and examined at 0 min, 30 min, and 120 min after venipuncture. The platelet counts in EDTA-anticoagulated blood examined at 0 min, 30 min, and 120 min after venipuncture were 111, 82, and 26×10^3/μL, respectively (Fig. 1A). These blood films showed agranular platelets (also called gray platelets) partly aggregated and normal granular platelets, middle-sized aggregated agranular platelets, and giant aggregated agranular platelets, respectively (Figs. 2A-C). On the other hand, platelet counts of blood collected with heparin and examined at 0 min, 30 min, and 120 min after venipuncture were 320, 329, and 288×10^3/μL, respectively (Fig. 1A). Similarly, platelet counts of blood collected with sodium citrate and examined at 0 min, 30 min, and 120 min after venipuncture were 333, 221, and 266×10^3/μL, respectively (Fig. 1A). All the heparin and sodium citrate blood films showed normal platelets. Based on these findings, the patient was diagnosed with pseudo-gray platelet syndrome (PGPS). On day 21 after admission, serotonin, a monoamine neurotransmitter stored in δ-granules of platelets and released in large amounts after platelet activation, was measured. The blood samples collected with EDTA and left for 30 min and 90 min after venipuncture were separated into platelet-poor plasma and other components by centrifugation at 3,000 rpm for 30 min at room temperature. The serotonin levels in the plasma of the patient, determined by high-performance liquid chromatography (Hitachi, L-6200, Tokyo, Japan), were found to be 59.0 and 147.4 ng/mL at 30 min and 90 min after venipuncture, respectively (normal value, <262.0 ng/mL) (Fig. 1B). The serotonin levels in blood samples of a normal control subject were also measured following the aforementioned procedure, and the levels were found to be 20.5 and 22.9 ng/mL at 30 min and 90 min after venipuncture, respectively (Fig. 1B). However, on mixing the EDTA-anticoagulated plasma of the patient with the platelets of the normal control subject, neither degranulation nor aggregation was found. On day 28 after admission, the AOSD was almost controlled with PSL (30 mg/day) in combination with TAC (2 mg/day) and the patient was discharged. Approximately 2 months after discharge, the platelet counts in EDTA-coagulated blood examined at 120 min after venipuncture was 208×10^3/μL without degranulation and aggregation on PSL (10 mg/day) in combination with TAC (2 mg/day) (Fig. 2D); in other words, an amelioration of