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BERNARD – SOULIER – LIKE FUNCTIONAL PLATELET DEFECT IN MYELODYSPLASTIC SYNDROME AND IN ACUTE MYELOBLASTIC LEUKEMIA ASSOCIATED WITH TRILINEAGE MYELODYSPLASIA*

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Platelet function was studied in a child with myelodysplastic syndrome (MDS: refractory anemia with an excess of blasts) and a child with acute myeloblastic leukemia (AML-M6) associated with trilineage myelodysplasia (TMDS). An acquired Bernard-Soulier-like platelet defect was considered in both patients with the findings of prolonged bleeding time and abnormally large platelets that failed to aggregate in response to ristocetin. In contrast to findings in von Willebrand's disease, the abnormal response of platelets to ristocetin could not be corrected by the addition of normal fresh plasma. The detection of abnormal platelet aggregation response to ristocetin may be a useful diagnostic finding for clonal disorders causing impaired platelet function in MDS and coexistent TMDS associated with AML. Further studies of ristocetin-induced platelet aggregation in a large number of these patients are required. *Key words: myelodysplastic syndrome, acute myeloblastic leukemia, Bernard-Soulier-like platelet defect.*

Myelodysplastic syndromes (MDS) are a heterogeneous group of clonal hemopoietic disorders in which defective maturation involves one or more of the hematopoietic cell lines. Although morphologic abnormalities of platelets are the most common findings, functional defects of platelets have been described in MDS in a limited number of studies[1-5]. Here we report Bernard-Soulier-like functional platelet abnormality in a child with MDS and a child with acute myeloblastic leukemia-M6 (AML-M6) associated with trilineage myelodysplasia (TMDS).

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Case Reports

Case 1

A 13-year-old girl presented with a two-year history of weakness, pallor and abdominal distention. There was no history of bleeding or exposure to cytotoxic drugs or radiotherapy.

Physical examination revealed an enlarged liver and spleen, which extended 6 and 15 cm below the costal margins, respectively.

A blood count showed a Hb of 6.58 g/dl, MCV 87 fl, WBC 4 x 10^9/L, neutrophils 60%, lymphocytes 26%, monocytes 8%, myelocytes 3% and blasts 3%. The platelet count was normal, but the peripheral blood smear revealed predominantly morphologically abnormal giant platelets and marked anisocytosis, poikilocytosis, hypogranular and Pelgeroid polymorphs. The bleeding time (Ivy) was greater than 15 minutes. Prothrombin and activated partial thromboplastin times were within the normal ranges.

The bone marrow aspirate was hypercellular and showed dyserythropoiesis and dysmyelopoiesis with eight percent myeloblasts and dysmegakaryopoiesis. Iron stores were increased with ring sideroblasts (15%). Cytogenetic analysis revealed a normal karyotype. A diagnosis of MDS (refractory anemia with an excess of blasts) was made according to the French-American-British (FAB) classification[6].

Case 2

A five-year-old girl was examined for weakness and abdominal distention which began six months prior to admission. The patient had no current bleeding problems or history of bleeding.

Physical examination revealed an enlarged liver and spleen, which extented 7 and 5 cm below the costal margins, respectively.

A blood count showed a Hb of 12.2 g/dl, MCV 72 fl, reticulocyte 3.2%, and WBC 40.2 x 10^9/L with 61% blasts, 3% myelocytes, 4% metamyelocytes, 11% neutrophils, 13% lymphocytes and 8% nucleated red blood cells. The platelet count was normal. Examination of peripheral blood showed numerous giant platelets and occasional micromegakaryocytes, anisopoikilocytosis, hypogranular and Pelgeroid neutrophils. The bone marrow aspirate was hypercellular with erythroid hyperplasia (55%) and showed dyserythropoiesis. Dysmyelopoiesis with 67% blasts (expressed as a percentage of the non-erythroid bone marrow cells) and dysmegakaryopoiesis were also noted. Bone marrow cytogenetic analysis revealed hypodiploidy, hyperdiploidy and tetraploidy in 36 evaluable metaphases. The HbF was abnormally high (46%). A diagnosis of AML-M6 was made, and trilineage myelodysplasia was considered based on the peripheral blood and

bone marrow morphology defined by the FAB group[6]. The patient's bleeding time (Ivy) was greater than 15 minutes. The prothrombin and activated partial thromboplastin times were normal.

Platelet Aggregation Studies

The patients had not taken any medications known to interfere with platelet function prior to this study. Venous blood was collected in a 0.1 M disodium citrate solution (9:1 blood to anticoagulant ratio). Platelet-rich plasma (PRP) was prepared by centrifugation at 150 x g for 10 minutes at room temperature and diluted with freshly prepared platelet-poor plasma (PPP) from the same subject to a final platelet concentration of 200×10^9/L. Platelet aggregation studies were performed on a aggregometer (chronolog Broomally, Pa, USA) at 37 °C. Aggregation was observed in 1 ml aliqouts under continuous stirring after the addition of adenosine diphosphate (ADP, Sigma 10^{-5} M final concentration), bovine tendon collagen (Sigma, 20 µl of standardized suspension) and ristocetin (Lundbeck, Copenhagen 1.2 mg/ml final concentration). The degree of aggregation was evaluated according to the percent aggregation (Tmax), which indicates the maximum percent change in light transmission of PRP after the addition of ADP, collagen and ristocetin.

The responses to ADP were normal; however, no ristocetin or collagen-induced platelet response was observed in either patient. The absence of platelet aggregation by ristocetin could not be corrected with the addition of normal fresh plasma. The patient data are presented in Table I.

Tablo I: Characteristics of Patients

Case No.	Age (yrs)/Sex	Diagnosis	Previous Bleeding History	Bleeding Time	Platelet Aggregation (T max %)		
					Ristocetin	Collagen	ADP
1	13/F	RAEB	No	> 15 min	NR	NR	N
2	5/F	AML-M6/TMDS	No	> 15 min	NR	NR	N

RAEB : Refractory Anemia Excess Blast.
AML-M6: Acute myeloid leukemia-M6.
N : Normal.
TMDS: Trilineage Myelodysplasia.
NR : No response.

Discussion

While thrombocytopenia is a common finding in MDS, functional platelet disorders have also been described in these patients. Prolonged bleeding time and poor response to ADP, epinephrine and collagen are the abnormalities that have been most frequently reported[2, 4, 7]. Furthermore, various degrees of decreased platelet aggregation rates by ristocetin have been reported in a few patients with MDS[2, 3, 5]. In addition, an acquired Bernard-Soulier-like platelet defect has been described in a child with coexisting primary MDS and monosomy 7[8]. A deficiency of platelet

membrane glycoprotein (GP) Ib-IX complex, and a weak agglutination response to ristocetin were documented in this case. In our patients, the platelet aggregation by ristocetin was absent. Although platelet membrane GP analysis of our patients was not available, an acquired Bernard-Soulier-like platelet defect was considered in light of the prolonged bleeding time and unusually large platelets that failed to aggregate in response to ristocetin. The abnormal ristocetin response could not be corrected with the addition of normal fresh plasma, which is also characteristic of the platelets of patients with Bernard-Soulier disease[9, 10]. These platelet abnormalities presented with no clinical bleeding in our patients, similar to that reported previously[5]. Although morphologic abnormalities of platelets are the most common striking feature in MDS, the ultrastructural observations of platelets are consistent with the possible presence of both normal and abnormal platelets in the peripheral blood[11]. The reason that variable degrees of abnormal or even normal ristocetin-induced platelet response could be detected in MDS is not clear[2, 4]. However, one explanation may be the variation in the number of abnormal platelets in the circulation, as was observed in a heterozygous state of Bernard-Soulier disease[12].

Although various defects in platelet function have also been described in leukemia[11], the abnormal platelet response to ristocetin in our patient with AML-M6/TMDS may indicate the possibility of an additional platelet defect in patients with AML coexistent with features of TMDS. Studies of ristocetin-induced platelet aggregation in a large number of these patients are needed. The detection of an abnormal aggregation response to ristocetin may facilitate earlier diagnosis of clonal disorders causing impaired platelet function in patients with MDS and patients with AML who have evidence of coexistent TMDS.

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