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Bengal macrothrombocytopenia is not totally an innocuous condition

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ABSTRACT

Inherited macrothrombocytopenia is a subgroup of thrombocytopenias, and is characterised by the presence of giant platelets and decreased platelet count with variable bleeding manifestations. Bengal macrothrombocytopenia is a newly described entity, previously called asymptomatic constitutional macrothrombocytopenia (ACMT), presented with variable bleeding tendencies; with mild to severe thrombocytopenia and macro-platelets in their peripheral blood smear and it is not totally an innocuous condition as described previously.

1. Introduction

Abnormal giant platelets are sometimes seen as an incidental finding in routine blood examinations, many of them are associated with acquired disorder such as idiopathic thrombocytopenic purpura (ITP) and myelodysplasia. In contrast inherited macrothrombocytopenia comprises a heterogeneous group of rare disorders, characterised by abnormal giant platelets, thrombocytopenia and bleeding tendency with variable severity; from no or mild bleeding tendency to severe bleeding diathesis and sometimes associated with syndromic features like renal failure, hearing loss and presenile cataracts. Many of these disorders share common clinical and laboratory features, making accurate diagnosis difficult and patients are often misdiagnosed and treated for idiopathic thrombocytopenic purpura (ITP). Bleeding syndromes that arise through an inherited defect of platelet production and giant platelets constitute a heterogeneous group of platelet disorders [1,2], some including the Bernard-Soulier syndrome (BSS) [3], MYH9 related macrothrombocytopenia (MYH9-RD) [4,5] and Mediterranean macrothrombocytopenias (MM) [6], sitosteroleamia/phytosteroleamia [7,8], the disease is caused by a mutation in either of the ABCG5 or ABCG8 genes which encode an ATP-binding cassette protein called Sterolin [9,10], a rare X linked GATA-1 associated macrothrombocytopenia has been associated with dyserythropoiesis and thalassemia [11] and Harris platelet syndrome (HPS) in healthy donors from West Bengal [12].

Inherited macrothrombocytopenias were previously considered to be relatively rare, but their prevalence is likely under estimated from complexities of diagnosis and spectrum of subclinical phenotype and limited knowledge is available about them, recent progress in the elucidation of the responsible genes for several inherited macrothrombocytopenias led to advances in understanding the pathophysiology and pathogenesis of the disease, however, in approximately half of the cases with inherited macrothrombocytopenia, the molecular cause remain unknown [13].

One of the first inherited giant platelet disorder associated with abnormal red cell morphology was found in Mediterranean Macrothrombocytopenia (MM) reported in healthy Mediterranean immigrants to Australia, which was associated with stomatocytosis, macrothrombocytopenia and splenomegaly. Harris platelet syndrome (HPS) is the most common giant platelet disorder to be described [14] so far in healthy blood donors from the north-eastern part of the Indian subcontinent (Bhutan, Nepal and Bangladesh) and is characterised by mild to severe thrombocytopenia, with giant platelets, absent bleeding symptoms and normal platelet aggregation studies.

2. Materials and methods

One hundred and twelve unrelated cases of macrothrombocytopenia were taken up for the study, who were referred to the Department of Haemostasis, National institute of Immunohaematology, Mumbai and Department of Haematology, NRS Medical College from 2009–2014, a few family members were also included. Diagnosis was confirmed on

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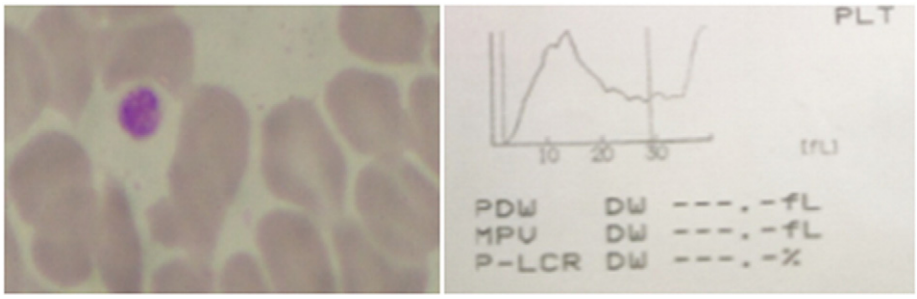

Fig. 1. Peripheral Blood Smear and platelet histogram showing the presence of giant platelets.

the basis of reduced platelet count ($<150 \times 10^9$/L) and mean platelet volume (MPV) which was greater than 10fl. Final diagnosis was confirmed by the presence of giant platelets in their peripheral blood smear evaluated by light microscopy (Fig. 1). All cases had normal anti-platelet antibody and ferritin levels [15]. The cases were grouped into three categories based on degree of thrombocytopenia i.e. mild ($100–150 \times 10^9$/L), moderate ($50–100 \times 10^9$/L) and severe ($<50 \times 10^9$/L). A detailed clinical history was taken for each case including the age of onset, marriage type, family history and type of bleeding, drug history etc. Pregnant females were excluded from the study.

Based on WHO bleeding scale, the severity of bleeding symptoms were segregated into grade 0 (no bleeding), grade 1 (petechiae), grade 2 (mild blood loss), grade 3 (gross blood loss) and grade 4 (debilitating blood loss). The study was approved by the ethics committee and undertaken in accordance with the ethical guidance of the institution involved. Written consent was obtained from all the cases before the collection of blood sample. Complete blood counts (CBC) were determined on blood samples collected in EDTA tubes using XT-2000i cell counter (Transasia Bio-Medical Ltd., Mumbai, India) within 30–120 min of collection. Repeated complete blood counts were performed on each case for at least four times in different times to see the reproducibility of platelet count and MPV. Peripheral blood smears were stained with modified Leishman's stain and evaluated by light microscopy.

2.1. Statistical analysis

Data were analysed using Prism 5 analyser (graphpad.com/scientific-software/prism/) using Spearman's rank correlation method. *P* values <0.05 were considered significant.

3. Results

All the cases had low platelet count (median, range) 89 (27–147 $\times 10^9$/L) and with high MPV 13.25 (12–18.5 fl), and showed the presence giant platelets without any inclusion bodies in their peripheral blood smear. The cases had low platelet biomass 0.84 (0.27–1.3), low haemoglobin 13.1 (10.1–16) and higher platelet distribution width 17.5 (14.1–18.9) as compared to controls (Table 1). There was no significant difference in MCV, MCHC, MCH and WBC between the cases and controls (Table 1).

The study included 55 females (Range: 8–70 years, Median age: 25 years) and 57 male (Range: 8–70 years, Median age: 30 years).

The distribution of cases were across India, the maximum numbers of cases were from West Bengal followed by other states, Maharashtra, Uttar Pradesh, Bihar, Orissa, Assam, Meghalaya, Kerala and one case was from neighbouring area Nepal (Fig. 2).

Severity of thrombocytopenia was varied among the cases; 45 had mild, 54 had moderate and 12 had severe thrombocytopenia, and only one had normal platelet count but was presented with giant platelets in peripheral blood smear.

According WHO bleeding scale 68 had grade 0 (Mild-30, Moderate-33, Severe-5); 6 had grade 1 (mild-2 and moderate 4); 18 had grade 2 (mild-10 and moderate-8); 16 had grade 3 (mild-2, moderate-9 and severe-5) and only 4 had grade 4 (moderate-1 and severe-3) bleeding score.

Majority of cases (61%) were asymptomatic and the major clinical manifestations were; 4% easy bruisability, 7% ecchymosis, 16% epistaxis, 5% frequent gum bleed, 10% menorrhagia and 6% had history of prolonged bleeding time after trauma. 12 had family history bleeding and 3 had transfusion history in the past. The laboratory findings which include complete blood count, screening coagulation, platelet aggregation and receptor study of 112 cases are included in Table 1.

4. Discussion

Platelet related bleeding disorders are either inherited or acquired, giving rise to bleeding manifestations of varying severity. Taking medical/drug history is the first step of diagnosis of any bleeding disorder and the best screening method for any platelet related disorder. Family history and age of onset of bleeding play a major role in differentiating inherited from acquired platelet function disorders, consanguineous partnerships increases the likelihood of a recessive platelet disorder. Screening coagulation tests; Prothrombin time (PT), activated partial

Table 1
Laboratory findings in cases with Bengal macrothrombocytopenia (BM).

Red blood cell indices median (range)		Platelet indices median (range)		Screening coagulation median (range)		Platelet aggregometry (%) median (range)		Receptor study (%) median (range)	
Hb gm/dL	A:13.1 (10.1–16) B: 14.1 (13–18.1)	Platelet Count ($\times 10^9$/L)	A: 89 (27–147) B: 186 (177–304)	PT (s)	A: 12.5 (11–13.9) B: 12.9 (12–14)	ADP (6 μM)	A: 63 (17–78) B: 89 (50–98)	GPIb (CD42b)	A: 75.3 (42.9–98.6) B: 90 (50–98)
MCV	A: 87.3 (64.4–95.6) B: 85.6 (65.1–94.8)	MPV (fl)	A: 13.25 (12–18.5) B: 10 (7.9–10.4)	APTT (s)	A: 28.6 (25–32) B: 29 (28–33)	Risto (1.25 mg/ml)	A: 75.5 (15–99) B: 80 (50–100)	GPIIb/IIIa (CD41a)	A: 80.5 (34.6–98.8) B: 89 (50–99)
MCH	A: 29.2 (19.6–32.0) B: 28.9 (20–31.8)	Platelet Biomass (%)	A: 0.84 (0.27–1.3) B: 0.98 (0.52–1.6)	TT (s)	A: 15.1 (12.9–18) B: 15.1 (15–19)	AA (0.75 mM)	A: 81.5 (10–98) B: 89 (50–100)	GPIX (CD42a)	A: 79.3 (27.3–98) B: 91 (50–98.2)
MCHC	A: 33.3 (30.1–35.4) B: 31.2 (31–34.8)	PDW (fl)	A: 17.5 (14.1–18.9) B: 16.5 (11.6–19.8)			Coll (4 μg/ml)	A:64 (47–90) B: 90 (50–99)		
WBC	A: 6.1 (3.4–9.8) B: 6.4 (3.5–9.5)								

A: Cases; B: Controls; PT: Prothrombin Time, APTT: Activated Prothrombin Time, TT: Thrombin Time, ADP: Adenosine diphosphate, Risto: Ristocetin, AA: Arachidonic Acid, Coll: Collagen.