Autosomal Dominant Thrombocytopenia with Microthrombocytes : A Family Study

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Summary

A family demonstrating autosomal dominant thrombocytopenia is described. A 28-year-old Malay housewife was found to have a platelet count of $40x10^9/l$ with a low mean platelet volume (6.8fl) while being investigated prior to ovarian cystectomy. The bone marrow was consistent with immune thrombocytopenia but she failed to respond to appropriate therapy. Five siblings, one parent and one nephew have easy bruising and platelet counts of $39\text{-}82x10^9/l$. Platelet aggregation studies excluded a major functional defect. Survival of homologous platelets in the circulation was normal. Familial thrombocytopenias are rare but important to differentiate from the common acquired thrombocytopenias in order to spare the patient unnecessary treatments.

Key Words: Cell size, Genetics, Platelets, Thrombocytopenia

Introduction

Thrombocytopenia is a common problem in young adults, especially women. In otherwise well people, the most likely diagnosis is 'idiopathic' (autoimmune) thrombocytopenia (ITP). In most adults, ITP is chronic but responds well to corticosteroids or splenectomy. The differential diagnosis of thrombocytopenia includes bone marrow failure or infiltration, megaloblastic anaemia, viral infection, microangiopathic haemolytic anaemia etc. However, in a generally well patient without anaemia or neutropenia, a diagnosis of inherited thrombocytopenia should also be considered. We present such a case, together with a study of her family, which highlights the need to consider this diagnosis and to take a full family history, especially in cases with a long history.

Case Report

The first presentation of the propositus was at another hospital, in 1988, at the age of 26 years, following the development of a petechial rash. However, she refused further investigation at that time. She presented again to that hospital with petechiae in 1990 and a bone marrow was performed, which was 'consistent with idiopathic thrombocytopenia'. She was treated with oral prednisolone, but her compliance was poor and she subsequently defaulted follow-up.

In 1992, she came to hospital again because of a large ovarian cyst requiring surgery. She was referred to this unit when her platelet count was found to be low. She gave a history of easy bruising throughout life, but there was no history of menorrhagia,

haemarthrosis, haematuria or excessive haemorrhage after either of her two normal deliveries. After one tooth extraction she had bled for about 3 hours. Investigations were as follows: Hb 13g/l, WBC 15.4x10^9/l (neutrophils 8.3, eosinophils 1.2, lymphocytes 4.5), platelets 40x10^9/l (mean platelet volume 6.8fl, expected[1] to be about 11-14fl at a platelet count of <100x10^9/l). The platelet count was the same in both EDTA and citrate, there was no platelet clumping on the film, and the platelet morphology by light microscopy was normal (no giant or agranular forms). Neutrophil morphology was normal: in particular there were no Döhle bodies. A bleeding time was greater than 20 minutes. Tests for anti-nuclear antibody and dsDNA antibody were negative; C3 and C4 were normal. A repeated bone marrow aspirate and trephine was hypercellular with plentiful megakaryocytes. There was a predominance of low ploidy megakaryocytes, but otherwise their morphology was normal.

An initial diagnosis of idiopathic (autoimmune) thrombocytopenia was made. She was treated with oral prednisolone 60mg per day for 4 weeks, but there was no change in the platelet count. She was given four doses of vincristine at weekly intervals, but the platelet count only dropped to 30x10^9/l. Antiplatelet antibody was screened for, but not detected, using an Immucor solid phase system with platelets as the captured antigen (courtesy of Dr Yasmin Ayob, Institute for Medical Research, Kuala Lumpur). So it was concluded that she did not have immune thrombocytopenia, and a careful family study (see below) showed that she was suffering from autosomal dominant thrombocytopenia.

Table I

(a) Aggregating agent	Concentration	Patient	Control
Adrenaline	5µmol/l	NIL	minimal
Collagen	4µg/l	5mm	8mm
ADP	5µmol/l	8mm	20mm
	2.5µmol/l	NIL	ND
Ristocetin	1.25µg/l	20mm	30mm
	1.00µg/l	10mm	30mm
	0.5µg/l	NIL	ND
(b) Aggregating agent	**Concentration**	**Patient**	**Control**
Adrenaline	5µmol/l	ND	40mm
Collagen	4µg/l	5mm	40mm
ADP	5µmol/l	10mm	37mm
	2.5µmol/l	NIL	37mm
Ristocetin	1.25µg/l	ND	ND
	1.00µg/l	ND	ND
	0.5µg/l	ND	ND

Platelet aggregation tests performed on the propositus. Results are expressed as mm of movement on the aggregometer tracing, where 40mm represents 100% aggregation. The tests were carried out using various aggregating agents at two different platelet concentrations: (a) with the control sample diluted in platelet-poor plasma to the same count as the patient (40x10^9/l), (b) with the patient sample concentrated up by spinning to a platelet count of 138x10^9/l. The control platelet count was 384x10^9/l. ND=not done

Platelet aggregation tests were performed and the results are presented in Table I. An attempt was made to control for the thrombocytopenia by either diluting the control platelets with plasma (Table Ia), or concentrating the patient's platelets by gentle centrifugation (Table Ib). The response to ristocetin appears to be normal, and there was no evidence for hyperaggregability. Aggregation responses were seen with collagen and ADP, but appear to be mildly reduced relative to control. Lack of response to adrenaline at low platelet count may not be significant, as the control also failed to respond at low platelet counts.

Her surgery was managed without bleeding complications by means of transfusion of 24 units of random donor platelets over a 9-day period. The corrected platelet increment was calculated from the formula[2]:

$$\frac{(P_1-P_0) \times \text{surface area } (m^2)}{\text{Number of units transfused}}$$

where P_0 and P_1 are the pre- and post-transfusion platelet counts respectively. This turned out to be 18.9 x 10^9/l, which is considered normal (mean 10x10^9/l, minimum 20x10^9/l)[3].

Homologous platelet survival was studied after a four unit platelet transfusion which was given two days before surgery commenced: the half-life of random platelets was about 40 hours. We were not able to study the survival of autologous platelets, because the relevant radio-isotopes (Cr^{51} or In^{111}) are not available here. Histology of the excised ovarian cyst showed a benign cystadenoma. There has been no change in her platelet count during a further year of follow-up.

Family Study

A family study was undertaken and the results are presented as a family tree in Figure 1: the pattern is consistent with autosomal dominant inheritance. The bleeding tendency was generally mild, as in the propositus. Subject II(a) had bled for 24 hours after a tooth extraction but had suffered no excessive postpartum haemorrhage after her 9 deliveries. Subject III(f) bled for 1-week after circumcision. Subjects III(b), III(e) and III(i) have only mild bruising tendencies. Subject IV(c) is asymptomatic. There was no family history of malignancy.

Discussion

As is typical in cases of mild genetic thrombocytopenia[4], our patient was initially misdiagnosed as suffering from ITP. However, the lack of response to prednisolone and vincristine led us to suspect an inherited thrombocytopenia. This was confirmed by the family study in which an autosomal dominant inheritance pattern was demonstrated. The autosomal dominant thrombocytopenias (ADT) include a number of well-characterised syndromes with associated abnormalities (e.g. May-Hegglin anomaly with Döhle bodies in the granulocytes[5], Alport syndrome with nerve deafness and nephritis[6]). The other ADT are heterogeneous, with normal, small or large size platelet, normal or abnormal function, and with variable megakaryocyte numbers, morphology and function[7]. Recently Najean and Lecompte described a new syndrome of ADT[4]. Their 54 patients with ADT had a normal platelet lifespan, normal platelet function, normal megakaryocyte numbers in the bone marrow, and an increased mean platelet volume (MPV). Electron microscopic and membrane glycoprotein studies were not performed, as in our case (we do not have the relevant facilities here). Clinically, their patients had mild bleeding tendencies and had usually been misdiagnosed as ITP previously. Eleven of them had been splenectomised without a rise in platelet count in any case. Although generally a benign condition, an increased incidence of leukaemia was noted in the affected families (4 cases from the 54 families studied). Our patient's condition is similar to their syndrome with her normal megakaryocyte numbers and morphology, but on the other hand she does appear to have mildly abnormal platelet function. However, the major difference is her MPV (6.8fl) which is definitely low, whereas in their series all the cases had an MPV greater than 10fl, corresponding to macrothrombia on the blood film. We were unable to study the survival of her own platelets in her own circulation, but homologous platelets survived well (half life 40 hours).

Unfortunately, our patient received ineffective therapy with both prednisolone and vincristine before the

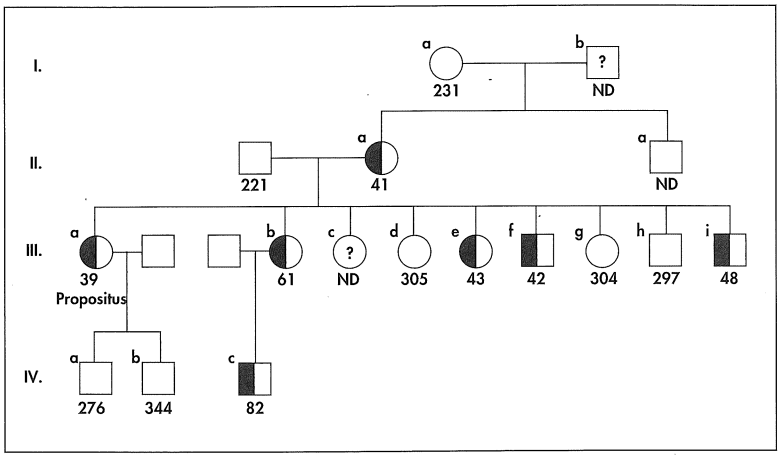

Fig. 1: The family tree of the propositus demonstrating autosomal dominant inheritance of thrombocytopenia. Numbers given are platelet counts (x 10^9/l). The mean platelet volume was 7-8fl in all affected family members. ND=not done.

correct diagnosis was made. The lack of anti-platelet antibodies in her serum was helpful in excluding ITP, and gave us confidence to proceed with her major surgery under platelet transfusion cover.

In conclusion, when a patient with apparent ITP has a very long history, has a positive family history, or fails to respond to standard therapy, an inherited thrombocytopenia should be considered even in the absence of clinical features of the well-known genetic thrombocytopenic syndromes.

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