Thrombocytopenia – radial aplasia (TAR) syndrome with associated immune thrombocytopenia

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Summary: We report a 10 year old girl with congenital thrombocytopenia with absent radii (TAR) syndrome. Unusually this patient has shown no abnormal bleeding tendency despite numerous orthopaedic procedures. There is evidence of an associated immune component to the thrombocytopenia which has not been previously documented.

Introduction

Thrombocytopenia with aplasia radii (TAR) syndrome was first completely defined as a clinicopathological entity in 1969. Since then it has been well documented with over 100 cases reported. The haematological findings are uniform with thrombocytopenia arising from hypomegakaryocytosis. Classical bony abnormalities include absent or hypoplastic radii and humeri and normal thumbs. We report a case with characteristic bony anomalies but, unlike previous cases, megakaryocytic hyperplasia and persisting thrombocytopenia which may be, in part, autoimmune in aetiology.

Case report

A girl was born in 1975 to a 49 year old man and a 36 year old woman after an uneventful pregnancy and delivery. Prior to this pregnancy the mother had experienced one previous spontaneous abortion in the first trimester and one normal delivery, a girl, who was developmentally normal. During the pregnancies she was taking phenobarbitone 300 mg twice daily for epilepsy. She subsequently delivered two normal girls. There was no family history of birth defects, haemostatic disorders or consanguinity.

Bilateral radial aplasia was diagnosed at birth, but haematological investigation was not performed. Three years later she presented to another institution with a progressive flexion contracture of her right knee which was treated with tibial osteotomy with no evidence of perioperative bleeding.

In 1985, when 9 years old, she presented to the orthopaedic unit with bilateral radial aplasia, hypoplastic humeri, flexion contractures of both knees and bilateral genu varum. There was no history of a bleeding diathesis and no liver, spleen or lymph node enlargement.

Investigations

An initial haematological screen showed haemoglobin 13.5 g/dl, reticulocytes 1%, leucocyte count 14.5 x 10^9/l with a normal differential count, platelets 30 x 10^9/l and direct antiglobulin test was negative. Coagulation investigations including prothrombin time, activated partial thromboplastin time and fibrinogen degradation products were within normal limits. A bone marrow aspirate was normocellular with a normal myeloid:erythroid ratio but megakaryocytic hyperplasia with occasional atypical forms. Platelet morphology was normal as assessed by light microscopy and automated platelet sorting with respect to shape and size. Electron microscopy of peripheral blood platelets showed a marked decrease in intracellular dense bodies compared to control platelets. Platelet function studies were also abnormal, with a prolonged bleeding time of greater than 20 minutes (normal range 2-7½ min) by the modified Ivy method, complete failure of platelet aggregation in response to collagen, and elicitation of primary aggregation waves only with ADP and adrenalin. Platelet

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kinetics utilizing indium labelled autologous platelets demonstrated a platelet recovery of 8% (normal 50–70%) at one hour with a half life of 32 hours (normal 110 hours). The platelet associated IgG (PAIgG) ratio was estimated to be 4.5, the normal value being less than 1.5. Briefly, this value is the ratio of IgG bound to the platelet membrane of the patient with respect to control platelets and corrected for the degree of thrombocytopenia. Other investigations included abdominal ultrasonography which showed marginal splenomegaly and crossed renal ectopia.

The lower limb deformities were treated by turn buckle casting and corrective osteotomies, over a 6 month period, to both tibiae and the right femur. The patient had no haemostatic problems and required no platelet transfusions. Since then she has remained well with no complaints.

Discussion

Thrombocytopenia with bilateral radial aplasia is an autosomal recessive disease with no evidence of parental consanguinity. It was initially thought to be a variant of Fanconi's anaemia but is now known to be a separate entity and some reports suggest it is more common. Spontaneous mutations may explain many of the cases and it is possible that the true incidence is higher than reported due to incomplete diagnosis or early death.

The subject of this report has both major groups of TAR anomalies, the first being the characteristic bony and soft tissue abnormalities, including absent radii (100% of reported cases) hypoplastic humeri (50%) and normal thumbs, the latter being a striking difference from Fanconi's anaemia. Soft tissue abnormalities are varied, including atrial/ventricular septal defects, cystic lesions of the pancreas, and urogenital anomalies. These latter features were not manifest in this girl apart from crossed renal ectopia which is a rare finding.

Haematological dyscrasias, especially thrombocytopenia, account for the second major group of abnormalities. Thrombocytopenia has been reported in 100% of cases, and is symptomatic in over 90% in the first 6 months of life, intracranial haemorrhage being a common initial presentation. The thrombocytopenia is due to decreased platelet production, a consequence of hypomegakaryocytosis, these precursors being abnormal, small, basophilic and vacuolated. Platelet counts and megakaryocyte number tend to approach normal as the patient approaches adolescence, although menorrhagia may remain a problem. In contrast to this typical course, the patient reported here has been asymptomatic since birth, even during surgical procedures and has required no platelet or red cell transfusions. These are required by the majority of reported cases during the first years of life. She is still frankly thrombocytopenic and marrow examination shows increased numbers of megakaryocytes of apparently normal structure. This suggests adequate platelet production and possible peripheral platelet destruction or sequestration as a partial or complete cause of persistent thrombocytopenia. To assess this further we performed several investigations on fresh platelets.

Ultrastructural and functional analyses of the platelets demonstrated a pattern consistent with δ-storage pool deficiency with a decreased number of platelet dense bodies and failure of normal platelet aggregation in response to collagen, ADP and adrenalin. This pattern was first described in TAR syndrome by Day & Holmsen and has also been reported in other inherited conditions such as Wiskott-Aldrich, Chediak-Higashi and Hermansky-Pudlak syndrome. Ours is only the third report of platelet functional abnormalities in TAR syndrome. It is due to a lack of ADP, ATP and serotonin in platelets and probably reflects a genetic relationship between absent radii and the storage pool defect. Platelet kinetic studies using labelled autologous platelets revealed evidence of decreased platelet survival with no evidence of splenic sequestration. This has been previously described in TAR but is also consistent with peripheral platelet destruction.

Autoimmune thrombocytopenia is a common cause of peripheral platelet destruction and we therefore measured PAIgG levels. Normally platelets have less than 10 ng of non-specifically bound immunoglobulin. In contrast this patient had almost 5 times this amount. Patients with autoimmune thrombocytopenic purpura (ATP) have 3 to 15 times this amount and patients with thrombocytopenia, such as SLE, often have elevated levels. The severity of autoimmune thrombocytopenia correlates with the level of bound platelet IgG and steroid therapy lowers the PAIgG ratio as the platelet count rises. Although it was thought that patients with ATP and raised PAIgG had an immune complex disease secondary to a possible viral hapten more recent evidence suggests that the immunoglobulin is directed at an autoantigenic platelet determinant consisting of a specific GPIb-GPIIIa-Ca²⁺ membrane complex. It is interesting to speculate that a similar antigenic determinant may be present on the surface of this patient's abnormal platelets and thus account for the increased destruction seen. Glanzmann's thrombasthenia, another congenital platelet disorder, is characterized by a complete lack of this complex. It will also be interesting to see whether this patient will respond to steroids or intravenous immunoglobulin if she requires platelet support in the future.

This case does not have any of the other haematological manifestations of this syndrome, such
as leukaemoid reactions or eosinophilia, the latter being associated with cows' milk allergy which has an increased frequency in this syndrome. Normocytic anaemia has also been described in a large number of cases and it is unclear whether this is due to blood loss or a shortened RBC lifespan secondary to haemolysis. This patient showed no evidence of this with a normal reticulocyte count and a negative direct antiglobulin test.

In summary, we report a case of TAR syndrome in which immune destruction may be the cause of the thrombocytopenia. It will be interesting to see if future cases have the same features.

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References

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