CASE REPORT

Congenital Amegakaryocytic Thrombocytopenic Purpura (CAMT)

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ABSTRACT

Congenital amegakaryocytic thrombocytopenia (CAMT) is a rare, autosomal recessive disorder induced by mutations of the gene coding for thrombopoietin (TPO) receptor (c-MPL) despite high levels of serum TPO. Patients initially present with isolated thrombocytopenia that subsequently progresses into pancytopenia. Although the mechanisms leading to aplasia are unknown, the age of onset has been reported to depend on the severity of the c-MPL functional defect. The primary treatment for CAMT is bone marrow transplantation. This report describes a newborn girl who presented to us with symptoms of sepsis but septic profile came negative except thrombocytopenia. Bone marrow biopsy was done for thrombocytopenia which revealed amegakaryocytic thrombocytopenia. She was given prednisolone.

Key Words: *Congenital amegakaryocytic thrombocytopenia (CAMT). Mutation. Thrombopoietin receptor. Pancytopenia. Bone marrow transplant.*

INTRODUCTION

Congenital amegakaryocytic thrombocytopenia (CAMT) is a rare autosomal recessive bone marrow failure syndrome that presents with severe thrombocytopenia which can evolve into aplastic anaemia and leukemia.[1-3]

The disorder is expressed in infancy with or without physical anomalies.[4,5] When they present without physical anomalies they are usually treated as sepsis, so strong clinical suspicion is needed with those patients who present without physical anomalies. In neonates and infants who are treated as sepsis and thrombocytopenia, failing to respond to antibiotic therapy, congenital amegakaryocytic thrombocytopenia should be kept in the differential diagnosis.

CASE REPORT

A newborn baby girl born to consanginous parents with normal antenatal history and birth events presented on second day of life with lethargy and reluctance to feed. On examination, she was lethargic but vitally stable and had normal systemic examination. Her baseline blood investigations, BSL and septic profile were done. She was started on first line antibiotics. Her preliminary results showed a normal BSL, slightly raised WBC count and a platelet count of 45 x 10^9/L which was initially thought to be a result of sepsis. Her cultures subsequently came out to be negative. She responded to the antibiotics well and was discharged with advice to complete the antibiotic course for 5 days and follow-up with a repeat CBC. Parents returned with the infant at 2 months of age with fever. Repeat CBC showed a WBC count of 61700 per cubic millimeter and a platelet count of 44 x 10^9/L. A provisional diagnosis of congenital thrombocytopenia was made and bone marrow biopsy was advised but the parents did not agree and left against medical advice.

The child presented at the age of 9 months in the outpatient with bruises on her body. There was no history of fever, lethargy, trauma or bleeding from any other site. She was a normally developed child with an up-to-date vaccination history. On examination, the baby had one bruise on the right side of her chest, one on anterior aspect of abdomen (Figure 1) and one on the dorsum of left foot. Rest of the general physical and systemic examination was unremarkable and she had no visceromegaly.

She was admitted and re-investigated and her CBC showed normal indices except a platelet count of 20 x 10^9/L. The peripheral smear showed anisocytosis, poikilocytosis, occasional fragmented RBC's and normal platelet morphology. The reticulocyte count was 3.2% and a direct Coombs test was negative. Coagulation profile came out to be normal as well. However, bleeding time was > 8 minutes.

Bone marrow examination was done which revealed severe megakaryocytic hypoplasia with thrombocytopenia consistent with amegakaryocytic thrombocytopenic purpura (CAMT). There was no evidence of lymphoma, leukaemia or metastasis on bone marrow aspirate.

The child is 11 months old now on regular follow-up and receiving prednisolone 1 mg/kg/day. Platelet range is between 25 x 10^9/L - 30 x 10^9/L.

Parents were counselled for bone marrow transplant but affordability and non-availability of HLA matched donor were the issues.

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Received: February 20, 2012; Accepted: March 22, 2013.

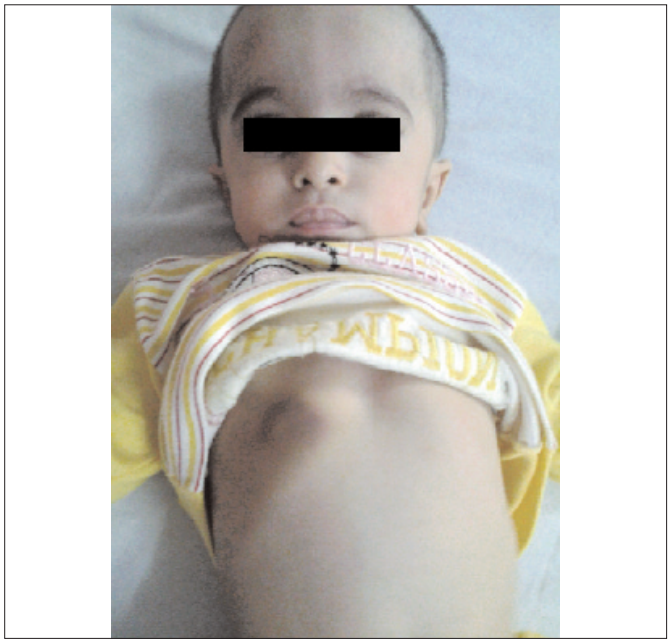

Figure 1: The bruising on anterior chest wall and upper abdomen.

DISCUSSION

The most common anomalies mentioned in literature are neurologic and cardiac. In central nervous system abnormalities like cerebellar, cerebral atrophy, micro-cephaly, and developmental delay are seen. In cardio-vascular atrial septal defects, ventricular septal defects, patent ductus arteriosus, tetralogy of Fallot, and coarctation of the aorta are seen, they can occur in combinations. Other anomalies include abnormal hips or feet, kidney malformations, eye anomalies, and cleft or high-arched palate.

Profound thrombocytopenia in an otherwise well newborn (< 10,000 platelets/L) should always raise the question of whether the baby has congenital amegakaryocytic thrombocytopenic purpura (CAMT).[6-8] The diagnosis is first entertained when an apparently well newborn develops easy bruising or bleeding soon after birth. Milder forms are sometimes discovered in the course of routine screening examinations. As with any recessive disorder, neither parent will have an abnormality of platelet count or function. A bone marrow examination will reveal markedly diminished or absent megakaryocytes with normal erythroid and myeloid series. However, later in the course of disease all cell lines are depressed once aplasia ensues. As in other inherited bone marrow failure syndromes, red cells may be macrocytic. Haemoglobin F may be elevated, and there may be increased expression of i-antigen on red-cells. CAMT is a progressive disorder, so even children with milder forms will develop worsening thrombocytopenia, as well as leukopenia and anaemia toward the end of the first decade of life. By the second decade, pancytopenia is likely to have developed.

Identified c-MPL mutation causing this disorder are 3 missense, 2 nonsense and 2 frame shift mutations. Homozygous for nonsense and frame shift mutation are expected to result in loss of c-MPL expression and cause severe form of disease (CAMT1). Mortality in these patients from bleeding, complication of aplastic anaemia, or leukemic transformation has been very close to 100%. Homozygous for missense mutation maintain residual activity of c-MPL leading to milder form type II.

A classification based on the course and outcome of the disease was proposed in 2005 supported by several other reports.[1,5] Type I has an early onset of severe pancytopenia, decreased bone marrow activity and very low platelet counts. In this group, there is complete loss of functional c-MPL gene. Median platelet count is usually 21 x 10^9/L or below.[5] Type II is the milder form with transient increases of platelet counts upto nearly normal values during the first year of life and onset of bone marrow failure at age 3 - 6 years or later. In this group, there are partially functional receptors for the c-MPL gene. Median platelet count is usually 35 x 10^9/L to 132 x 10^9/L. In type III, there is ineffective megakaryo-poiesis with no defect in the c-MPL gene.

The differential diagnosis for severe congenital thrombocytopenia includes thrombocytopenia with absent radii syndrome (TAR),[9] Wiskott-Aldrich syndrome (WAS), neonatal alloimmune thrombocytopenia and Fanconi's anaemia. Diagnostic features of amegakaryotic thrombocytopenia include defective signal and response to thrombopoietin in megakaryocyte-colony formation, so megakaryocytes do not proliferate inspite of elevated serum level of TPO.[1,4] Decreased numbers of erythroid and myelocytic progenitors in clonal cultures are seen with lack of MPL mRNA in bone marrow monocellular cells hence no reactivity to TPO by the haematopoietic progenitor cells. A gradual decrease in white blood cells and red blood cells occurs with age. There is no reactivity to TPO by the haematopoietic progenitor cells.[1] The surface expression of the TPO receptor MPL is absent. Bone marrow is hypoplastic without dysplasia.

Preliminary studies showed that the prognosis of CAMT patients becomes poor when tri-linear marrow aplasia develops in childhood.[5] Treatment options for CAMT are limited. Supportive care with unrelated donor platelet transfusions and minimum transfusion are recommended. Decision to transfused platelets should be on bleeding episodes and not the platelets counts.

Desmopressin acetate (DDAVP) should be avoided in small infants due to the risk of hyponatremia but may be useful in older children and adults in bleeding episode. Avoidance of non-steroidal anti-inflammatory medications and aspirin, steroids and immunoglobulins do not have an effect on thrombocytopenia.

For aplastic anaemia, androgens in combination with corticosteroids may induce a temporary partial response,

but the effect is short-lived and does not prevent mortality. Cytokine therapy with interleukin-3 and granulocyte-macrophage colony-stimulating factor shows transient responses.[1]

Bone marrow/Stem Cell Transplant is the only treatment that ultimately cures this genetic disease.[10] It has been planned for this case and the patient is currently being managed with corticosteroid therapy.

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