Case report:

Congenital dyserythropoietic anaemia type 1: A case report from central India.

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Abstract :

Congenital dyserythropoietic anaemias (CDAs) are a heterogeneous class of inherited disorders resulting from abnormalities of erythropoiesis and distinctive morphologic abnormalities in bone marrow erythroblasts[1]. Dyserythropoiesis is the main reason for anaemia but shortened half life of red blood cells may also contribute to the anaemia. Mainly four types of CDAs are identified depending on bone marrow morphology,clinical features and genetic variants. Additional subgroups and variants are also identified. We are reporting a case of six months old male child presented with severe anaemia diagnosed with CDA type1. CDA type 1 is rare autosomal recessive disorder and only more than 300 cases are reported worldwide. Very few are reported from India. We are reporting a case of CDA type 1 from Vidarbha region of Maharashtra from a tertiary care centre.

Keywords: Congenital dyserythropoiesis anaemia type1, Bone marrow, dyserythropoiesis

Case Report :

A six month old male child first by birth order born by non-consanguineous marriage presented to us with complaint of paleness for 20 days and fever since 3 days. No history of acute bleeding. No previous history of blood transfusion. Child was exclusively breastfed and developmentally normal. Weight as 6kg, length- 64cms and head circumference was 42cms. On examination, heart rate-140/min, respiratory rate- 42/min, facial puffiness and peripheral oedema was present. Child had pallor. On systemic examination, per abdomen child had non tender soft hepatomegaly with liver span of 7cm and no splenomegaly. Other systemic examination was normal.

On investigations, Hb- 2.8gm/dl, RBC-0.76 millions/mcl, WBC- 16,700cells/ml and platelets-1,15,000 cells/ml. Mean corpuscular volume was 94fl. Peripheral smear was showing anisopoikilocytosis with predominant normocytic normochromic RBCs with presence of macrocytosis. Liver function tests showed serum total bilirubin 2.70 mg/dl with unconjugated bilirubin- 1.6 mg/dl, AST-60U/L,ALT-17U/L and alkaline phosphatase-83U/L. Serum electrolytes and creatinine were in normal range. Serum ferritin was high (975 ng/dl) and reticulocyte count -12.5 with corrected reticulocyte count of 2.4%. Vitamin B12 deficiency was ruled out.High performance liquid chromatography was negative for hemoglobinopathy. Ultrasonography of abdomen also showed no gall stones.

Bone marrow examination was done which showed hypercellularity with erythroid hyperplasia. Erythropoiesis was megaloblastic showing features of dyserythropoiesis in the form of nuclear budding, micronucleus, multinuclearity and multipolar mitosis. Erythroblasts were showing chromatin bridges. Occasional red blood cells showed basophilic stippling. Hence the diagnosis of congenital dyserythropoietic anaemia was made. Acidified serum lysis test (HEMPAS) was negative. Genetic study was not available.

Diagnosis of CDA type 1 was done due to early age of presentation with megaloblastic cells on peripheral smear and internuclear chromatin bridges between erythroblasts on bone marrow examination and negative HEMPAS which is diagnostic of CDA type 1.Child was transfused packed red cells and symptomatic treatment was given.

Child has been following with us after discharge and has required transfusion on follow up.

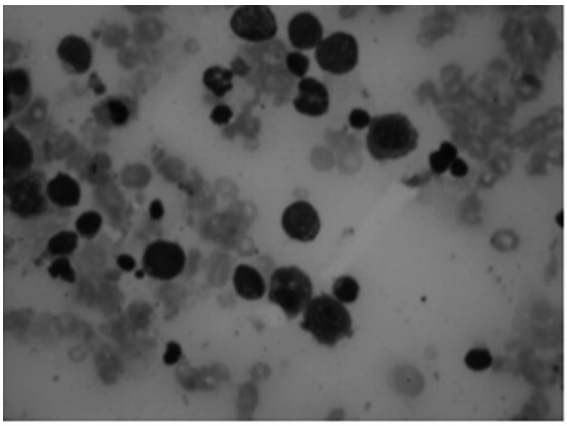
Discussion:

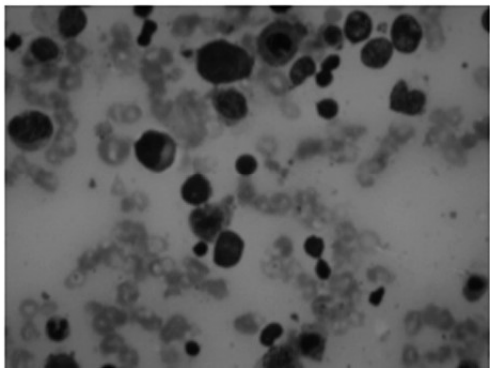
Congenital dyserythropoietic anaemia are inherited disorders resulting from abnormalities of late erythropoiesis causing ineffective erythropoiesis and secondary hemochromatosis. Four major forms of CDA and several minor subgroups have been identified[2]. CDA should be considered in differential diagnosis if suboptimal reticulocytosis is present for the degree of anaemia and unexplained hyperbilirubinemia with iron overload is present. CDA type 1 and 2 are autosomal recessive whereas type 3 and 4 are autosomal dominant in inheritance. Incidence of CDA type 1 is 1 per 100000 births per year[3]. More than 300 cases are reported worldwide till now[4]. CDA I is a rare clinical entity that has been reported mainly from the Central and Western European countries and North Africa with very few cases reported from Indian Subcontinent[5].

It is autosomal recessive disorder caused due to mutation in CDAN1 gene on chromosome 15 and mostly diagnosed in childhood or adolescence[6]. Clinical manifestations vary from anaemia to jaundice, hepatomegaly or splenomegaly. Due to dyserythropoiesis, extramedullary haematopoiesis in paravertebral areas or frontal and parietal bones of skull may occur. Dysmorphic features in the form of syndactyly, supernumery toes or absence of nails may be present in 4-14% of patients with CDA type1. In CDA type1, laboratory findings include low haemoglobin with inadequate reticulocyte counts for the degree of anaemia. Bone marrow aspirates showing erythroid hyperplasia with multinuclearity and basophilic stippling along with polychromatic erythroblasts. Incompletely divided cells with chromatin bridges is highly specific finding in CDA type1. The pathognomonic finding of RBCs lysis in acidified serum of CDA type 2 is absent in CDA type1.It is called HEMPAS (hereditary erythroblastic multinuclearity with a positive acidified serum test). Electron microscopy is the gold standard for diagnosis of CDA type1 which reveals characteristic swiss cheese pattern of heterochromatin.

The treatment of CDA type1 is mainly supportive including red cell transfusion. Transfusion requirements may be reduced by treatment with Interferon-±. Gallstones may require cholecystectomy in children. The most important long term complication of hemosiderosis may occur even in un-transfused children as a result of increased intestinal absorption of iron along with iron deposition due to ineffective erythropoiesis. Repeated phlebotomy result in normal ferritin levels and children may require oral chelation therapy when serum ferritin levels rises above 1000ng/dl.

Differential diagnosis of CDAs include megaloblastic anaemia, hemoglobinopathies including thalassemia and myelodysplasias. In our case, megaloblastic anaemia was ruled out by absence of loose and ûne chromatin structures of erythroblastic nuclei and giant granulopoietic cells and hyperlobulation of megakaryocytes along with normal serum vitamin B12 levels. Normal high performance liquid chromatography ruled out hemoglobinopathies. Chromatin bridges with





Bone marrow smear – megaloblastic erythroblasts showing multinuclearity and nuclear budding with chromatin bridges

megaloblastic erythroid hyperplasia favoured CDA type I along with negative HEMPAS test and ruled out other CDAs.

Conclusion : CDA I should be suspected in all children with refractory anaemia, hepato-splenomegaly, erythroid hyperplasia and features of dyserythropoiesis in marrow examination. Hyperbilirubinemia and iron overload without any reason also raises the suspicion of CDAs. The diagnosis of CDA I can be made from typical peripheral blood smear and bone marrow examination characteristics.

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