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Pathology

CONGENITAL DYSERYTHROPOETIC ANAEMIA TYPE-I (CDA-I) – A CASE REPORT

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ABSTRACT Congenital dyserythropoeitic anaemia type-1 is a rare autosomal recessive disorder characterized by macrocytic anaemia, megaloblastoid erythroid hyperplasia with dyserythropoeisis, distinctive nuclear abnormalities in the erythroblast, decreased reticulocyte count for the degree of anaemia and transfusion dependency of varying degree. In a few instances, somatic malformations have been described. Cholelithiasis may also be associated with this condition. Etiology of CDA-1 is not fully understood but most cases have been associated with mutation in the CDAN1 gene (15q15.2). Here we report a case of CDA- 1 in a male child of 3yrs presenting with fever and loose motion of 2weeks duration at JNIMS, Porompat. On clinical examination, severe pallor, hepatospleenomegaly, mild jaundice and mild frontal bossing are present. Blood picture show pancytopenia, increased MCV, macrocytosis, basophilic stippling and moderate anisopoikilocytosis. Bone-marrow examination reveals erythroid hyperplasia with megaloblastoid changes, features of dyserythropoeisis, binuclearity and trinuclearity, internuclear chromatin bridges, double nucleated with different nuclear size and increased iron store. The laboratory findings are increased unconjugated bilirubin, increased serum ferritin, increased urinary urobilinogen and negative acidified serum test. Treatment consists of blood transfusion and iron chelation, interferon therapy, spleenectomy and B.M transplant on individual patient basis.

KEYWORDS : Congenital dyserythropoetic anemia (CDA), Dyserythropoesis, HEMPAS.

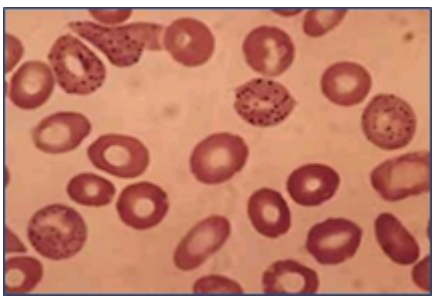
Introduction:

Congenital dyserythropoetic anaemias comprise a group of very rare hereditary disorders characterized by ineffective erythropoeisis as the predominant cause of anaemia and by distinct morphological abnormalities of the erythroblast in the bone marrow.[1] Three major subgroups desnignated types I, II & III and several minor subgroups have been identified on the basis of morphological and serological characteristics. CDA I and II are autosomal recessive while CDA III is autosomal dominant. CDAs of the three classical types are defined on the basis of bone marrow morphology. Wickramasinghe et al described a CDA type IV, morphologically type II but with negative serum tests, sharing bone marrow morphology of CDA type III. CDA I has abnormalities of chromatin structure, CDA II displays marked increase in bi-and multi-nucleated erythroblasts in the bone marrow and CDA III shows giant multinucleated erythroblast and was first reported in 1962. CDA type I is a rare autosomal recessive disorder [2] and some patients have consanguineous parents. It is characterized by macrocytic anaemia, megaloblastoid erythroid hyperplasia with dyserythropoeisis, dinstinctive nuclear abnormalities in the erythroblast consisting of two segments, double or triple nucleation and thin chromatin bridges between pairs of erythroblasts which may also seen between two nuclei in one cell.[1,3,4] Decreased reticulocyte count for the degree of anemia and transfusion dependency of varying degrees. A few patients may be born with somatic malformations which include brown skin pigmentation, syndactyly, absence of phalanges and nails in fingers and toes, short stature etc.In some patients akin to thalassemia major, severe erythroid hyperplasia, may cause marked widening of diploic space leading to parietal and frontal bossing. 169 cases from 143 families with CDA I worldwide were recorded in literature till Dec 2011.Most families were from western Europe and middle east countries but sporadiac cases were also reported from Japan, USA, India and China.[1,5] CDA I is caused by mutation in the CDAN1(15q15.1-15.3) and C15 or F41 genes(15q14).[6] It is usually diagnosed in childhood or adolescence although the condition can be detected before birth in some cases.[7] CDA I precipitated by pregnancy have also been reported.[8] Spleen is palpable in 80-90% of the cases. Mild jaundice and symptoms due to gallstones may be present.

CASE REPORT :

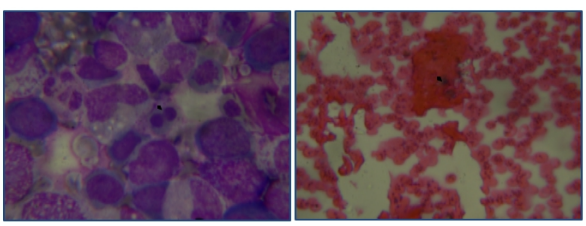
A 3 year old male child presented with fever and loose motion of 2 weeks duration at JNIMS, Porompat. There was associated dull aching abdominal pain around the umbilical area. The patient had received 1 unit of packed cell after admission. He had history of similar episode and had received ½ unit of blood transfusion. He used to have frequent fever and coryza.On physical examination he had severe pallor, mild jaundice, mild frontal bossing and mild hepatospleenomegaly.His haemoglobin was 3.8gm%.Serum bilirubin and serum ferritin were raised. Acidified serum test was negative. His peripheral smear examination and bone marrow aspiration was done.In peripheral smear erythrocytes showed macrocytosis with few tear drop shaped poikilocytes, basophilic stippling and moderate degree of anisopoikilocytosis. Leucopenia with few atypical lymphocytes and thrombocytopenia were also seen. Reticulocyte count was 1.8% . MCV was 101 fl.

Fig. 1:- Basophilic stippling



Bone marrow smears showed hypercellularity for the age due to erythroid hyperplasia. M:E was 1:1. The erythroid precursors showed megaloblastoid features with features of dyserythropoiesis like nuclear bridging, binucleation and trinucleation. Many erythroid cells smudges were seen. Leucopoeisis was reduced with normal maturation. Lymphocytosis and mild eosinophilia were also seen. Megakarypoeisis was reduced with normal platelet formation.Bone marrow iron store was increased (WHO-Grade IV).

Fig: 2



A.Internuclear chromatin bridge B.Iron stain(Perl's stain)

DISCUSSION:

CDAs should be suspected in any person with chronic anaemia.

Ineffective erythropoiesis with low absolute reticulocyte count for the degree of anaemia despite erythroid hyperplasia in the marrow. Differential diagnosis : Thalassemia, some hemoglobinopathies, hereditary sideroblastic anemia, myelodysplasia, megaloblastic anemia (mainly B12 or folate deficiency) and other forms of CDA.In this case there is macrocytosis with dyserythropoeisis ,commonly not observed in thalassemia or hemoglobinopathy. Sideroblastic anemia is ruled out as there is absence of ringed sideroblasts as well as absence of microcytic blood picture. No dysplastic features on the granulocytic/ megakaryocytic lineage rules out myelodysplastic syndrome.Absence of loose and fine chromatin structures of erythroblastic nucleated giant granulopoetic cells and hyperlobation of megakaryocytes ruled out macrocytosis (mainly B12 or folate deficiency).[4,7,9] Acidified serum lysis was normal which ruled out CDA II.No giant erythroblasts were observed which ruled out CDA III.[4] All the above findings favored a diagnosis of CDA type I though confirmation is by identification of biallelic pathogenic variants in CDAN1 or C15 or F41. Prognosis of CDA-1 is usually good even if the life expectancy is slightly reduced. Morbidity related iron overload like congestive cardiac failure, arrhythmias, diabetes and chronic liver disease (cirrhosis) can be fatal. So strict monitoring for iron overload is recommended.

CONCLUSION:

CDA I should be suspected in children with refractory anemia, hepatosplenomegaly, jaundice, reticulocytopenia, erythroid hyperplasia and features of dyserythropoiesis in marrow examination. The diagnosis of CDA I can be made with high reliability from diligent analysis of peripheral blood and technically appropriate specimens of aspirated bone marrow and other laboratory parameters with clinical co-relation.

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