

**CONGENITAL DYSERYTHROPOIETIC ANEMIA: CASE REPORT OF THREE
CASES**

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Abstract

Congenital dyserythropoietic anemias (CDA) belong to a group of inherited disorders which are characterized by maturation arrest during erythropoiesis and an inappropriate reticulocyte production in contrast with erythroid hyperplasia in the bone marrow. They show specific morphological abnormalities which allowed for morphological classification of these conditions termed CDA type I and II. With advances in genetic analysis, some altered proteins were found to be involved in chromatin assembly, such as codanin 1 in CDA type I and SEC 23B in CDA type II. CDA type III was characterized later with presence of gigantoblast in the bone marrow. However, even in the absence of genetic analysis CDAs can be diagnosed if history of patient, clinical examination and profile is taken into account and a high index of suspicion is maintained if specific morphological abnormalities are found in the bone marrow and peripheral blood.

Keywords: dyserythropoiesis, CDA, inherited anemias

Introduction

The congenital dyserythropoietic anemias comprise a group of very rare hereditary disorders characterized by ineffective erythropoiesis and by distinct morphological abnormalities of the erythroblasts in the bone marrow¹. The classification proposed in 1968² is still used today. The morphological hallmarks of the erythroblasts are not per se specific, but may also be observed as single abnormalities in other disorders of erythropoiesis¹.

The term was first used by Crookston et al for cases later classified as CDA II³ and by Wendt and Heimpel for cases later classified as CDA I². CDAs of the three classical types are defined on the basis of bone marrow morphology. This classification is still used in clinical practice⁴. CDA type I and II are autosomal recessive disorders with CDA having abnormalities of chromatin structure, CDA II displays marked increase in bi- and multi- nucleated erythroblasts in their bone marrow. In contrast CDA type III, first reported in 1962, is autosomal dominant

disorder showing giant multinucleated erythroblasts⁵.

However, there are many families that fall within the general definition of CDAs but do not conform to any of the three described classical types. Wickramasinghe et al described a CDA type IV, morphologically CDA type II but with negative serum tests, sharing bone marrow morphology of CDA type III. This group also comprises: CDA with prominent erythroblastosis, CDA with intraerythrocytic inclusions, CDA with thrombocytopenia and CDA without dysplasia⁶.

Epidemiology of CDAs

169 cases from 143 families with CDA type I and 454 cases from 356 families with CDA type II worldwide were recorded in the literature till Dec 2011. Hence CDA II is three times more common as compared to CDA I. Most families are from western Europe and middle east countries, but sporadic cases were also reported from Japan, USA, India and China⁷⁻⁹.

The true frequency of CDA types I and II is most probably higher than estimated. This could be due to diagnostic difficulties and clinical complexities and heterogeneity, as demonstrated by the observation that in these inherited disorders the correct diagnosis is often delayed until adulthood⁴.

Case 1

A one year old male child presented with progressive pallor since three months of age. He was a product of consanguineous marriage (1st cousins) hailing from Afghanistan and required blood transfusion since four months of age. There was no

family history of similar illness. Direct questioning revealed delayed milestones. On examination he was found to have marked pallor and hepatosplenomegaly. There was no jaundice, cyanosis or lymphadenopathy. There were no skeletal abnormalities. His investigation profile is tabulated in table 1.

Case 2

14 year old male hailing from Punjab, India presented with generalised weakness, fatiguability and progressive pallor requiring blood transfusions since past 10 years. Requirement of transfusions had increased for past four months. On examination he was found to have marked pallor, jaundice and hepatosplenomegaly. There was no cyanosis or lymphadenopathy. There were no skeletal abnormalities. His investigation profile is tabulated in table 1.

Case 3

30 years old male hailing from Merut (Uttar Pradesh, India) presented with history of recurrent jaundice, weakness, easy fatiguability, vomiting on & off for eight years duration. There was history of epistaxis three years back. Direct questioning revealed episodes of jaundice lasting three months and five months. Present episode of jaundice had been lasting for four months. There was no history of bleeding from any site or blood transfusion. Examination revealed pallor, jaundice, marked hepatosplenomegaly. There was no cyanosis, clubbing, oedema, lymphadenopathy or sternal tenderness. There was no evidence of bleeding tendencies. His investigation profile is tabulated in table 1.

Table 1

SNo	PARAMETER	CASE 1	CASE 2	CASE 3
1	Hb (gm/dl)	4.1	4.1-9.2(with transfusion)	7.9
2	TLC (thousand/ μ l)	8200	5400	5500
3	Platelet	2.1	3.1	2.7

	(lakh/ μ l)			
4	S. Iron (mg/dl)	355220	230	250
5	TIBC (mg/dl)	300	276	250
6	%Tfr Stauration (%)	73.3	100	100
7	HAMs test	negative	negative	negative
8	Heinz Bodies	negative	negative	negative
9	G6PD def test	negative	negative	negative
10	TORCH Analysis	negative	negative	negative
11	Hb Electrophoresis (Patient)	Hb F : 5% HbA2 : 2.8 %	Hb F : 0.4% HbA2 : 2.2 %	Hb F : 0.6% HbA2 : 2.2 %
12	PBS study	macrocytes preponderance polychromasia ++ No NRBCs	anisopoikilocytosis fragmented RBCs spherocytes + tear drop cells +	anisopoikilocytosis basophilic stippling thromia cells
13	Bone marrow Aspirate study	ME ratio : 1:2 Dyserythropoei sis + Gigantoblasts seen	ME ratio : 1:3 features of dyserythropoei sis seen Nuclear bridging seen	ME ratio : 1:3 Megaoblastic maturation Dyserythropoei sis seen in form of nuclear bridges, unequal nuclear division
14	Bone marrow Biopsy Study	hypercellular erythroid hyperplasia megaloblastoid erythropoiesis	hypercellular erythroid hyperplasia - bi nucleated erythroid cells seen	hypercellular erythroid hyperplasia - bi nucleated erythroid cells seen
15	Hb Electrophoresis (father)	- HbA2 : 2.2%	- HbA2 : 2.3 % -Hb F : 0.8%	HbA2: 1.7%
16	Hb Electrophoresis (mother)	- Hb A2 : 2.0 %	HbA2 : 3.8 % Hb F : 0.7%	HbA2: 2.6%
17	PNH Test	Negative	negative	negative

The three cases described above shared few common findings. All had anemia and hepatosplenomegaly. There were no bleeding tendencies. There was no evidence of iron deficiency anemia or haemolytic anemia. Investigations for common viral

markers were negative. Peripheral blood smear study revealed anisopoikilocytosis. Bone marrow study showed reversal of ME ratio with features of dyserythropoiesis. Test for PNH was negative.

Discussion

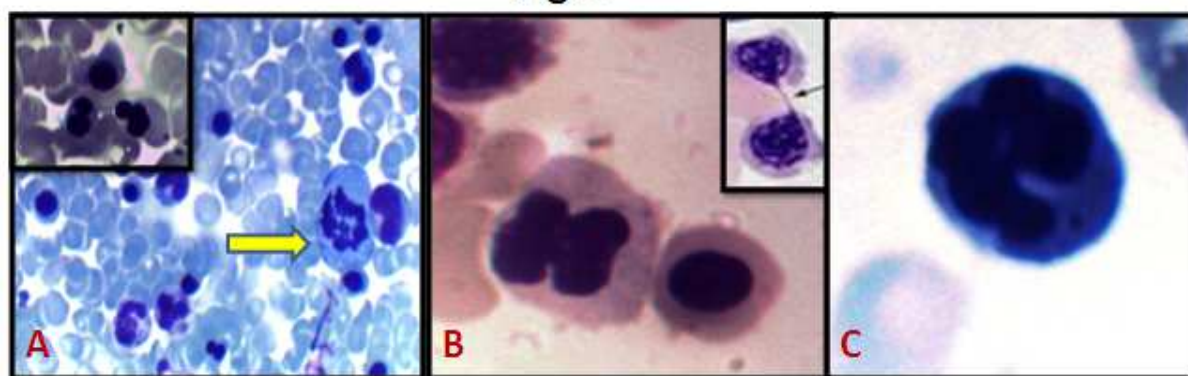
The correct diagnosis of congenital anemias is often delayed¹⁰. Many hematologists or clinical pathologists have never seen a case of CDA and do not recognize the well known morphological abnormalities or because, by misinterpretation of clinical and laboratory findings, a bone marrow study is not performed¹. On the other hand, the diagnosis of a congenital dyserythropoietic anemia is often erroneously suspected because the observer overvalues the presence of abnormalities that can be seen in the CDAs but also in other more common red cell disorders. If an appropriate technique of preparation of bone marrow is used, hypercellularity can be recognized, and is always seen in histobiopsies^{1,4}. The relative frequency of red cell precursors in the bone marrow is increased, with a mean E:M ratio of 4 and 8 times the normal in CDA I and CDA II. Our cases showed EM ratio of 0.28-0.5 (mean- 0.37). Previous experience in normal adults showed a range of 0.2 -1.0, corresponding to data on 50 and 67 adults published by Bain et al¹¹ and den Ottolander et al¹² respectively. These investigators found a range of 0.2-0.9 (mean 0.42, 95% confidence limits 0.2- 0.9)

and a range of 0.24-0.80 (mean 0.46, 95% confidence limits 0.42-1.2), respectively.

Our cases had anemia, jaundice and hepatosplenomegaly with hypercellular bone marrow with marked dyserythropoiesis. Same was described by Renella et al¹³ in her study of CDAs

Case 2 and 3 revealed a hypercellular marrow with erythroid hyperplasia (fig 1A) and features of dyserythropoiesis in the form of internuclear bridges (fig 1B), nuclear budding and occasional unequal nuclear division (fig 1a,b). The clinical picture of CDA I includes varying degrees of anemia, jaundice and hepatosplenomegaly. Most patients have lifelong anemia with haemoglobin between 7-11 gm/dl. Bone marrow shows 30-60% early and late polychromatic normoblasts with extreme abnormalities of size and shape. Small number of cells are bi- and multi-nucleated^{4,13}. The hallmark of CDA I is incompletely divided cells with thin chromatin bridges between erythroblasts. These abnormalities are most specific changes, usually present in more than 20% of cells^{2,4}.

Fig 1



Case 1, a one year old child whose bone marrow examination revealed giantoblasts (fig 1C) in the bone marrow evaluation, was a likely case of CDA III. He presented with progressive pallor and transfusion

dependence at early stage. This disorder is the rarest form of CDAs, having been described in approximately 40 individuals, most of which are members of single large

Swedish family¹⁴. The gene for the same has been localised to chromosome 15q21-q25¹⁵. To conclude the diagnosis of CDA can be made with high specificity from clinical profile and morphological analysis by light microscopy alone even in the absence of expensive genetic analysis (if not available), when aberrations of the erythroblast nuclei like bi- / multi-nucleation, unequal division, internuclear bridges, gigantism, karyorrhesis etc are present in more than 20% of erythroid series of cells. Common causes of haemolytic anemias should be excluded.

Conflict of interest

All authors have none to declare

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