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Congenital dyserythropoietic anemia type I - A Case Report

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Abstract
Congenital dyserythropoietic anemia (CDA) is a rare disease globally. It is characterized by marked dyserythropoiesis as the name suggests. There are only a few hundred cases of Type- I CDA described sporadically. Here we are presenting two cases of CDA –I which were diagnosed based on a simple examination of bone marrow after ruling out common mimickers. One of our patients presented in the neonatal period while the other child presented at the age of six months. Bone marrow examination of both patients showed dyserythropoiesis, and binucleated erythroblasts with much of karyorrhexis. CDA- type II, paroxysmal nocturnal hemoglobinuria was ruled out among other diseases. Genetic tests could not be done. After diagnosis, both patients were put on lifelong blood transfusion therapy and subsequently on iron chelation for treating iron overload secondary to repeated transfusion. Genetic counseling was done in both cases and a bone marrow transplantation option was offered to both families but could not be done due to the non-availability of matched donors and financial constraints. Both patients are still on regular follow-up from our center and growing well. Our case report highlights the fact that this rare entity of congenital dyserythropoietic anemia can be reliably diagnosed even in a resource-poor setting using a simple investigation of bone marrow examination.
Keywords: Congenital dyserythropoietic anemia, Children, Diagnosis

Introduction

Congenital dyserythropoietic anemias (CDA) are rare inherited disorders of erythropoiesis; characterized by ineffective erythropoiesis with multi-nuclearity and karyorrhexis and refractory anemia with subsequent hemosiderosis due to repeated transfusion. Three major types of CDA, designated types I, II, and III have been identified based on morphological and cytogenetic characteristics. Type two is the commonest one but the prevalence of CDA type I is not known due to the rarity of the disease. There are only isolated case reports available to date and more than 100 cases of CDA type I have been described in literature. As the presentation is clinically similar to that of hemolytic anemia which is a more prevalent hematological disorder, this disease can be easily missed if not evaluated properly. This disease is rare globally and from India, there are only a few case reports (1,2) available.

Case Report

Case 1

The patient presented to our hospital in the neonatal period at 15 days of life with severe pallor. The child had already received multiple blood transfusions since day one of life at other health facilities. He was a product of a non-consanguinous marriage and developmentally normal with no dysmorphic features. On examination, he had hepatosplenomegaly and severe pallor. Congenital infection and hemolytic anemia were kept as differential diagnoses. His TORCH profile was normal. He had mild indirect hyperbilirubinemia. The hemogram showed hemoglobin of 5 gram/decilitre, mean corpuscular volume (MCV) of 110 fl, reticulocyte count of 1.2%, and peripheral smear did not reveal any abnormality. The osmotic fragility test was normal and Glucose-6-phosphate dehydrogenase deficiency (G6PD) was also ruled out. The patient received a blood

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transfusion and was discharged. However, the patient again developed severe anemia within one month of discharge. As there was relative reticulocytopenia, bone marrow aspiration and biopsy were planned. A bone marrow examination was done at the age of 2 months which showed marked dyserythropoietic and karyorrhexis. Erythroid precursors also showed inter-nuclear chromatin bridges. Many binucleate erythroblasts were also seen. Myeloid and megakaryocytic precursors were normal. No gigantoblasts were seen which ruled out the possibility of CDA type III. The findings were suggestive of CDA type I. Acidified serum lysis test done was negative ruling out CDA type II. Screening for PNH was done which was negative. Hemoglobin electrophoresis was also normal which was done on follow-up later on at the age of one year. So based on the typical clinical course, hepatosplenomegaly, and typical bone marrow findings a diagnosis of congenital dyserythropoietic anemia was made. Cytogenetic studies were not done due to lack of availability. The patient is still on regular transfusion and also receiving chelation for hemosiderosis.

Case 2

The patient was a male child who presented to us at 6 months of age with severe anemia and hepatosplenomegaly with mild jaundice. He was also born into a non-consanguinous marriage with a normal neonatal period. After the age of 4 months, he received multiple red cell transfusions before coming to our hospital. At admission, the child was severely pale with mild icterus and hepatosplenomegaly. The patient had a hemoglobin level of 5 gram/ decilitre, MCV of 108 fl, and reticulocyte count of 0.5%. Peripheral smear was normal. High-pressure liquid chromatography (HPLC), Direct Coombs test (DCT), and osmotic fragility were normal which ruled out hemolytic causes. So, for etiological diagnosis bone marrow examination was done which revealed a similar picture as described in our first case. There were features of florid dyserythropoietic along with many binucleate erythroblasts with internuclear chromatin bridges with absent gigantoblasts. Megaloblastic and myeloid precursors were essentially normal in maturation. The acidified serum lysis test was negative and PNH was also ruled out. The patient also had normal levels of vitamin B12 and folate. Based on typical marrow findings diagnosis of type I CDA was made. This patient is also under our regular follow-up and on regular blood transfusion and chelation therapy. Bone marrow transplant could not be done due to lack of matched siblings.

Discussion

In the normal marrow, approximately 3-5 cells out of 1000 erythroblasts are abnormal; however, normal individuals do not display multi-nucleated or pluripolar mitosis. CDA is mainly divided into three subtypes. Type I has megaloblastic and binucleated erythroblasts with internuclear bridges (2% - 5%). Type II erythroblasts have multinuclearity of late erythroblasts with karyorrhexis in around (10 % - 40%) while type III has gigantoblasts in (10 % - 40%) where erythroblasts have more than 8 nuclei (3). Type II is further distinguished from the other types by serologic and ultrastructural abnormalities. This rare entity is autosomal recessive in inheritance in type I and II while autosomal dominant in type III can present in variable age groups ranging from childhood to adulthood.

Differential diagnosis includes hemoglobinopathies like thalassemia, hereditary spherocytosis, megaloblastic anemia, myelodysplasia, and sideroblastic anemia. As dyserythropoiesis and karyorrhexis can also be found in nutritional anemia, leukemia, and hemolytic anemias it is very important to

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rule out these entities thoroughly before considering this rare diagnosis of CDA (4). Mutations of the CDAN1 gene have been implicated in the causation of CDA- I. CDA I is thus two to three times less frequent than its counterpart, CDA II. CDA-I has also been observed among North Africans, Saudi Arabians, Japanese, Indians, and the Chinese population (5). Heimpel et al. have followed up 21 cases of CDA type 1 from 19 families for 37 years since 1967 which is one of the largest series till date. Among them, all had chronic macrocytic anemia while 2 individuals required regular transfusion, and four developed gallstones before 30 years of age. Mutational analysis showed at least one allele from exons 6 to 28 within CDAN1 in fifteen patients (6). CDA Registry of North America (CDAR) has started to enroll patients of CDA to study the natural history of CDA and to create a repository to aid in research of the pathobiology of this rare disease. 47 patients have been enrolled so far and out of them, 7 have CDA-I due to biallelic CDAN1 mutations. They all presented with perinatal anemia and required transfusions during the infantile period (7).

Dysmorphic features may be present in 4-14% of patients of CDA type –I, though none of our patients had any of the dysmorphic features like syndactyly, supernumerary toes, skin hyperpigmentation, and short stature among many other features.

CDA though a rare diagnosis should always be considered in cases of refractory anemia with hepatosplenomegaly and erythroid hyperplasia with features of dyserythropoiesis. Even without cytogenetic testing or mutational analysis, CDA can be reliably diagnosed based on typical clinical course and bone marrow findings. Bone marrow examination has been the gold standard for diagnosis (8). Goede JS et al., reported two cases of CDA-I morphologically compatible and genetically confirmed with bone abnormalities and responded well to treatment with alpha-interferon and the researchers documented the association of skeletal anomalism with CDA I (9). In our cases, we could not do genetic testing and alpha-interferon was not available to us due to economic constraints.

Conclusion

Our series of two rare cases of CDA-I carries an important message that this rare disease can be diagnosed reliably once we are clinically aware of this entity through a simple test of bone marrow examination.

Ethical Consideration

No ethical rule violation was done. Written informed consent was taken from parents of the children for publication. No image or identifying features have been published

Author's contributions

SR and DS were involved in the diagnosis, management of both the children and preparing the manuscript.

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Conflict of interest

The authors had no conflict of interest to declare.

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