CASE REPORT

A case report of rare disease from Bangladesh: Congenital Dyserythropoietic Anemia (CDA) type 2, with thrombocytopenia

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Rahman S. A case report of rare disease from Bangladesh: Congenital Dyserythropoietic Anemia (CDA) type 2, with thrombocytopenia. J Blood Disord Treat. 2023;6(1):1-4.

ABSTRACT

The Congenital Dyserythropoietic Anemias (CDAs) consist of a group of rare hereditary disorders of erythropoiesis, characterized by ineffective erythropoiesis and distinct morphologic abnormalities of the majority of erythroblasts in the bone marrow. The three classical types of CDAs have been defined on the basis of bone marrow morphology. This working classification is still used in clinical practice. The subcategorizing are CDA type I, CDA type II and CDA type III. There are, however, families that fall within the general definition of the CDAs, but do not conform to any of the three classical types. CDA type IV, CDA variants: CDA with prominent erythroblastosis after splenectomy, CDA with intra erythrocytic inclusions, CDA with thrombocytopenia and, finally, the very rare form of CDA without dysplasia.

Keywords: Erythroblasts; Bone marrow; Congenital dyserythropoietic anemia; Hereditary disorders

INTRODUCTION

CDA I is characterized by megaloblastic changes, ineffective erythropoiesis and nuclear abnormalities of erythroblasts including a "swiss cheese" aspect of erythroblasts on electron microscopy. The typical morphological ultrastructural studies accompanied by negative acidified serum lysis and adult I/l agglutination test constitute the major diagnostic features. CDA types I and II are autosomal recessive diseases. Conversely CDA III is a more heterogeneous disorder consisting of subtypes with an autosomal recessive trait or sporadic occurrence. Patients show diserythropoesis with giant multinucleated erythroblasts. In most cases anemia is mild and does not require transfusions. In contrast to other types of CDA no relevant iron overload can be noticed.

CDA II is the most common subtype of CDA where patients may present and diagnosed at birth, during childhood or during young adult life. Patients often have few or no symptoms. Symptoms of anemia are present in some cases but the extent of anemia varies markedly from case to case and some are not anemic. Jaundice is present in 90% of cases, moderate to marked splenomegaly in 70% and hepatomegaly in 45%. Gall stones may develop because of increased pigment turnover secondary to the ineffectiveness of erythropoiesis and, in some patients, also due to a reduction in red cell life span. Some patients may present with complications of severe iron overload such as cirrhosis of the liver, cardiac haemosiderosis and diabetes mellitus. Less common complications of CDA type II include posterior mediastina tumors composed of haemopoietic tissues' and an aplastic crisis secondary to a parvovirus infection [1].

CDA II exhibits autosomal recessive transmission. Since its inception, the molecular pathogenesis of CDA II was not fully defined and was thought to be owed predominantly to defects in glycosylation of the red cell membrane proteins band 3 (anion exchange protein transporter 1) and band 4.5 (glucose transporter 1). However, in recent studies, investigators have demonstrated that CDA II is caused by missense mutations in the SEC23B gene encoding Coat Protein Complex II (COPII), complex proteins critical for membrane homeostasis and vesicular trafficking from the endoplasmic reticulum to the golgi complex in eukaryotes. Disrupatiention of SEC23B gene expression has been shown to recapitulate the nuclear cytokinesis and double cell membrane defects characteristic of CDA II erythroblasts.

The classification of congenital dyserythropoietic anemia's was done on the basis of characteristic changes of bone marrow cytology. Bone marrow samples show distinct hyper cellularity due to erythroid hyperplasia with 45%-90% erythroid precursors. In CDA II, 10 to 45 percent (mean 20%) of all erythroblasts are bi and multinucleated. If characteristic erythroblasts are present the diagnosis of CDA II is very likely. The current "gold standard" for diagnosis of CDA II is bone marrow biopsy in conjunction with laboratory tests. We present a case of CDA II diagnosed in a 38-year-old man who presented with moderate anemia, splenomegaly, hypersplenism followed by splenic infraction. This study was approved by the local research ethics committee. Written informed consent was obtained from the patient [2].

CASE PRESENTATION

On mid-January 2019, a 38 years old male presented with fatigue, anorexia, weakness and lumpy feeling in the upper abdomen and admitted into Medinova Specialized hospital, Feni. His fatigability was increasing day by day and lumpy feeling of upper abdomen was gradually getting enlarge. Primarily, major clinical findings were moderate anemia with splenomegaly (mild) and diagnosis was hereditary hemolytic anemia (thalassemia). Though there was no relevant family history or consanguinity of marriage. To confirm the diagnosis CBC, Hb electrophoresis, iron profile and other investigations were done. Investigation reports turns out, this case was not suggestive of hereditary hemolytic anemia. In Hb electrophoresis, Reduced Hb A2 was found. CBC showed Hb 7.4 mg/dl, total RBC count 2.9×10^6/mcl, total platelets count 160×10^3/mcl, total WBC count 8.8×10^9 mcl, differential count (neutrophils 62%, lymphocytes 30%, monocytes 6%, eosinophils 2%), HCT/PCV-27%, MCV 90.6 fl, MCH 24.8 pgm, MCHC 27.4 g/dl, reticulocyte count 10.74%. Iron profile report showed, iron 320 mcgm/dl, ferritin 69.88 ng/ml, TIBC 401 microgram/dl, Serum folate 20 ngm/ml. interestingly, his S. bilirubin level was little high 2.3 mg/dl. So, we planned thorough history taking and relevant investigations to find out the actual cause of anemia with splenomegaly. Note that, in the meantime patient's moderate anemia was corrected by given two unit of whole blood and patient was clinically improved. Due to economic issue involved with further evaluation, patient asked for preparation time and he was then discharged with medication and advised for readmission two weeks later [3-5].

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Received: *01-Jun-2020, Manuscript No. PULJBDT-20-2646*; **Editor assigned:** *05-Jun-2020, PreQC No. PULJBDT-20-2646 (PQ)*; **Reviewed:** *19-Jun-2020, QC No. PULJBDT-20-2646*; **Revised:** *02-Jan-2023, Manuscript No. PULJBDT-20-2646 (R)*; **Published:** *30-Jan-2023, DOI: 10.37532/puljbdt.2023.6(1).1-4.*

On his readmission on March, 2019 we searched for actual cause of anemia with splenomegaly. This time his general examination showed, he was moderately anemic (again), lethargic with normal vital parameters. Abdominal examination revealed mild splenomegaly, mild hepatomegaly. So we investigated all possible causes of hepatosplenomegaly and blood disorders relevant in context to our country/region. Hematological investigations Coomb's test (direct/indirect negative), PBF (Leukoerytroblastic blood picture with thrombocytopenia), were performed followed by bone marrow examination which was not conclusive. Other serological, microbiological and biochemistry investigations (attached below) did not help to come up with a definite diagnosis. Even CT whole abdomen with contrast indicates nothing but moderate splenomegaly with calcification and mild hepatomegaly. Note that, symptomatic treatment of the patient was going on along with another one unit of human whole blood transfusion for which anemia was corrected but abdominal distension of the patient due to splenomegaly was not ameliorating. So therefore, we decided to reinvestigate his bone marrow examination in Dhaka (CLD/HCC and other diseases like hematological malignancy, chronic mararia, Kalazar were excluded earlier through other investigations).

Bone marrow aspiration on 19th July 2019 in Dhaka, finally helped to capture the disease, as it showed, hyper cellular marrow, erythroid hyperplasia (myeloid/erythroid ratio 1:2 and diserythropoesis which highly suggested Congenital Dyserythropoietic Anemia (CDA), type II with thrombocytopenia probably due to hypersplenism. However, definitive investigation genetic testing for CDA was not done due to unavailability in Bangladesh. As hypersplenism could explain anemia and thrombocytopenia in CDA we further advised the patient to test CT whole abdomen with contrast again. But this time due to financial condition of patient, investigation was not possible. However, as recurrent anemia was developed splenomegaly was increasing, we advised and prepare (with all prophylactic vaccination pneumococcal, meningococcal and haemophilus influenza) the patient for splenectomy on September 2019, but he refused for the procedure. However, he continued for talking folison, hydroxycarmamide, thalidomide for next 7 month as prescribed by the physician [6-8].

On 2 May, 2020 he developed severe abdominal discomfort as well as abdominal distension due to massive splenomegaly with sudden development of massive ascites and severe anemia, (Hb-5.3 gm/dl). This time all investigations were repeated, interestingly we have new findings of high S. bilirubin from normal range (3.1 mg/dl), with S. albumin 3.1 gm/dl, S. ferritin 369 microgm/l and Alpha Feto Protein (AFP). He was admitted in hospital and given 6 unit of blood transfusion. On the following day patient felt mechanical respiratory distress due to massive ascites and emergency ascites fluid aspiration was done; 4 liters of ascetic fluid mixed with fresh blood was withdrawn. Not only that, patient need continuous blood transfusion to maintain his Hb level and oxygen saturation. Emergency CT abdomen with contrast showed mottled increased attenuation of the spleen suggesting haemorrhagic infarction with massive ascites. We did endoscopy of upper GIT to find out portal hypertension (varices) in favor of chronic liver diseases and found no varices. Moreover, we exclude CCF by NT pro BNP (normal), pulmonary HTN by echocardiography (normal). Thus we exclude the chance of developing complication of secondary hemochromatosis. However, we also exclude liver malignancy by Alpha Feto Protein (AFP) test. Therefore, finally diagnosis was CDA type 2 with hypersplenism with splenic infarction and emergency Splenectomy was planned (Table 1).

Table 1: Investigation findings data.

Investigation findings	
ESR	20 mm/1st hour
Reticulocyte count	10.74%
Serum vit B12	304 pg/ml
TSH	1.99 miu/l
Uric acid	7.8 mg/dl
LDH	232 U/l
HBsAg	Negative
Anti HBc (total)	Negative
Anti-HCV	Negative
Bilirubin (total)	1.0 mg/dl
SGpatient	32
ApatientT	32.3 sec
Patient	12.4 sec
INR	1.03
Creatinine	0.96 mg/dl
ICT for malaria	Negative
ICT kalazar	Negative
Anti HIV 1, 2	Negative
CT whole abdomen with contrast	Moderate splenomegaly with calcification and mild hepatomegaly
Endoscopy of upper GIT	No features of portal hypertension (varices)
GGT	13.1 IU/L

ALP	91 IU/L
Total protein	7.9 gm/dl
Serum albumin	3.9 gm/dl
Serum globulin	4.0 gm/dl
A:G ratio	1
G 6PD assay	20.8 U/gm Hb
Osmotic fragility test	Negative

RESULTS AND DISCUSSION

CDA II is also known as Hereditary Erythroblast Multinuclearity with a Positive Acidified Serum test (HEMPAS), familial benign erythroblast polyploidy and hemolytic splenomegalic erythropolydyskaryos. CDA II is an autosomal recessive disorder. The anemia in CDA II was initially thought to be due to ineffective erythropoiesis secondary to the glycosylation defects of red blood cell membrane proteins. Recent studies have demonstrated that missense mutations in SEC23B gene are responsible for the disease. These mutations result in the impaired expression of COPII proteins which are essential for functional golgi processing in erythrocytes [9].

Although many CDA II patients are diagnosed in their infancy or childhood, some patients, as in our case, remain unrecognized until late adulthood (34 years) likely due to less severe anemia in early age. However, In CDA there is special verity of anemia characterized by ineffective erythropoiesis and resulting from a decrease number of RBCs in the body and a less than normal quantity of hemoglobin in the blood. This shortage prevents the blood from carrying an adequate supply of oxygen to the body tissues. The resulting symptoms can include tiredness, fatigue, weakness, pale skin and splenomegaly. Apart from these, most affected individual have jaundice, an abnormal buildup of iron causes secondary hemochromatosis due to Iron overload which can lead to arrhythmias, congestive cardiac failure, diabetes and chronic liver disease (cirrhosis). These features are seen in other more common inherited hemolytic anemia's also. Therefore, clinical presentation in these patients could lead to misdiagnosis such as hemolytic anemia, thalassemia, hereditary spherocytosis or iron deficiency anemia and as consequence, to inappropriate therapies [10].

Our case presented with features of anemia and splenomegaly, clinically jaundice was absent (though S. bilirubin was 2.3 gm/dl) with no features of Iron overload. Primarily patient was misdiagnosed as a case of thalassemia, but later on serological/hematological, bio chemical test exempt previous diagnosis and finally bone marrow aspiration revealed presence of a large number of multinucleate and bi nucleate erythroblasts in the bone marrow and typical morphological abnormalities of the membrane of circulating erythrocytes. Bone marrow findings are gold standard but identification of specific mutant gene is confirmatory which was not available to us. In the absence of availability of molecular studies, a diagnosis of CDA type II was made based on clinical, laboratory and characteristic bone marrow findings and exclusion of other broad differential diagnosis. However, autoimmune hemolytic anemia was discarded as the direct Coombs test was negative. The hemoglobin electrophoresis test was normal except for reduced Hb A2 was found. The tests for glucose-6-phosphate dehydrogenase were negative [11].

The morphologic Findings of the Peripheral Blood (PBF) in CDA II patients are often highly nonspecific. In our case, PBF showed moderate anisochromia with some anisopoikilocytosis with target cell, ellipatientocyte and ovalocyte, occasional cremated and contracted cells, few fragmented cells including schistocytes, platelets gradually reduced with normal morphology (from 160×10^3/mcl-90×10^3/mcl), prompted bone marrow biopsy to rule out a marrow infiltrative process. The characteristic feature in the bone marrow in CDA II is erythroblast nucleation with equal size of the two nuclei. The nucleation is usually present in more than 10% of erythroblasts and is typically restricted to late polychromatophilic or orthochromatophilic erythroblasts. Karyorrhexis is common and multi nucleation may also be present diagnosis of CDA II in our case was based on the characteristic bone marrow findings of hyper cellular marrow, erythroid hyperplasia (myeloid/erythroid ratio 1:2 and electron microscopy showed binuclearity, internuclear bridging and many partially degenerative erythroblast with disrupted cytoplasm which highly suggested Congenital Dyserythropoietic Anemia (CDA), type II. Bone marrow finding also suggested thrombocytopenia probably due to hypersplenism. However, further diagnostic test including a positive serum acidification (Ham) test, a SDS-PAGE Red Blood Cell (RBC) membrane electrophoresis (that reveals a narrow and fast migrating band 3), confirmatory test, molecular genetic analysis to identify a SEC23B mutation were not done due to unavailability in our region [12].

In bone marrow examination, interestingly, we found thrombocytopenia, which was explained as due to hypersplenism. However, this might be a case of very rare variety of CDA variant, (special verity other than classical CDAs) CDA with thrombocytopenia (CDA type II like). We did not consider the diagnosis as because in gold standard bone marrow examination we found distinct morphological change in fevour of CDA type II: Bi-neuclearity among majority of the erythroblast (>35%). Moreover, we did not have enough facilities to test gene sequencing for GATA1 gene, confirmatory for CDA variant or chromosomal test to identify specific chromosome (Xp11.23) for CDA with thrombocytopenia. Therefore, our final diagnosis was CDA type II with thrombocytopenia [13,14].

However, common clinical findings in CDA type II, apart from anemia and splenomegaly, are clinical Jaundice and features of Iron over load. Jaundice is measured by increased level of S. bilirubin (both direct and indirect) than normal range in blood. On the contrary, Iron overload is measured by serum ferritin and Iron level (iron profile). Serum ferritin levels increase with time in both untransfused and transfused patients, irrespective of the HFE H63D genotype, suggesting that increased erythropoiesis is the primary cause of iron over. Moreover, due to secondary hemochromatosis, iron absorption increases in response to ineffective erythropoiesis and secondary erythroid hyperplasia. In our case, the patient did not have clinical jaundice on first presentation (though S. bilirubin 2.3 mg/dl was little high). It developed after years (S. bilirubin 3.1 mg/dl) when there was sudden development of massive ascites. Similarly S. ferritin and S. iron were in normal range initially but increased with time. It may be due to rapid progression of disease process in late phase was masked, in developing iron overload [15,16].

Splenectomy is the treatment procedure for effective improvement of chronic anemia in CDA type II. Splenectomy leads to moderate to sustained increase in Hb concentration shown in 48 patients published in case reports [17,18].

So we recommend splenectomy for our patient after confirmation of diagnosis but patient refused. Later on, as disease progressed, patient developed severe anemia due to hypersplenism and active intra-abdominal bleeding due to splenic infraction. So, finally we recommend emergency splenectomy. Now we can conclude that even though these disorders are chronic and incurable correct and aggressive management can improve the quality of life as well as life span [19,20].

CONCLUSION

In summary, CDA type II, the most common subtype of the CDAs, may be a potential cause of long standing anemia in adult patients and present with anemia, splenomegaly, rarely with thrombocytopenia (hypersplenism). Moreover, hypersplenism followed by splenic infraction resulting in massive hemorrhagic ascites is very uncommon. Elective splenectomy should advise to improve Quality of Life Years (QALY) for affected patients.

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