Congenital dyserythropoietic anaemia type II in a teenager presenting with severe anaemia

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SUMMARY

Congenital dyserythropoietic anaemia (CDA) type II is a rare disease characterised by inefficient erythropoiesis and mononuclear cytopenia. Patients generally present with extravascular haemolytic anaemia, jaundice and splenomegaly. A female patient in her mid-teens presented with severe anaemia and abdominal distention. Medical history was significant for the diagnosis of β-thalassaemia intermedia made in her infancy. However, subsequent investigations showed normal reticulocyte counts that were disproportionate to the severity of her anaemia and a negative β-thalassemia mutation analysis, leading to concerns about a specific lineage disorder. A bone marrow trephine showed features typical of CDA type II-erythroid hyperplasia with multiple binucleate erythrocytes. CDA type II has often been mistaken for other congenital or acquired forms of anaemia; this case report intends to raise awareness among clinicians to consider CDA type II as a rare but possible cause of severe anaemia in a teenager with a previous presumptive diagnosis of β-thalassaemia .

BACKGROUND

Congenital dyserythropoietic anaemias (CDAs) are a group of hypoproliferative anaemias characterised by ineffective erythropoiesis.[1–4] The most studied variety in this category is CDA type II. The prevalence data of CDA type II is unavailable due to its rarity; however, over 300 cases have been reported in literature. CDAs collectively remain mainly undiagnosed and are often mistaken for other congenital or acquired forms of anaemia.[3 4] The diagnosis of CDA is often made in childhood with diagnostic workup done in lieu of reticulocyte counts disproportionate to the anaemia.[1–4] CDA type II has an autosomal-recessive mode of inheritance, with congenital defects at the locus of CDAN2 impairing the coded protein SEC23B. This protein has an important role in the assembly of the midbody during cytokinesis.[1]

Clinical features are variable depending on the degree of ineffective erythropoiesis. Historically, CDA type II has been known by many names: familial benign erythropoietic polyploidy, haemolytic-splenomegalic-erythopolydyskaryosis and hereditary erythroblastic multinuclearity with positive acidified serum lysis test.[1 3] As described by its synonyms, virtually all patients with CDA type II have pallor and hepatosplenomegaly with peripheral smear studies showing normocytic anaemia with normal to mildly raised reticulocyte counts.[1–4] Diagnosing CDA type II requires a trephine biopsy, which may show binuclearity with erythrocyte hyperplasia in conjunction with laboratory tests ruling out other causes of dyserythropoiesis.[1 3]

CASE PRESENTATION

A female patient in her mid-teens presented as a referral to our emergency department with abdominal distention, pedal oedema and easy fatiguability for the last 2 weeks. Medical history was significant for the diagnosis with β-thalassaemia intermedia when she was an infant, and has since required regular blood transfusions (six packed cell volumes per year prior to current admission). The patient reported that she missed her last four blood transfusions due to financial constraints. The patient belonged to a rural impoverished community. Medical history and laboratory data are mentioned in table 1.

The patient was born to a consanguineously married couple (second degree). There was no history of recent deaths or known blood disorders within the family.

The patient had a pulse rate of 84 bpm, a blood pressure of 100/60 mm Hg and a temperature of 36.1°C. On examination, the patient had facial puffiness, severe pallor, mild icterus and raised jugular venous pressure. The abdomen was distended, the liver was palpable under the right costal margin and the spleen was located midway between the xiphisternum and the pubic symphysis, and was hard in consistency. With these features of icterus, anaemia and hepatosplenomegaly, a wide differential list including extravascular haemolytic diseases and hepatitis were made.

INVESTIGATIONS

The patient's profile was negative for hepatitis antigens and antibodies. Further evaluation was necessary to confirm β-thalassaemia and rule out myelodysplastic syndromes and abdominal tubercular granulomatous bleeding (endemic). The results of the laboratory investigations are as seen in table 2.

Radiological investigations including a contrast CT of the abdomen showed massive splenomegaly with regenerative benign liver nodules (figure 1).

The bone marrow biopsy showed numerous binucleate erythrocyte precursors (>30% of observed erythroblasts) with binucleation distinctly visualised, by two equal-sized polychromatophilic erythroblasts with equal size nuclei, under H&E stain through multiple sections. Occasional

Table 1 Medical history and laboratory parameters

Data from previous hospitalisations	Clinical data	Inference	Outcome
Hospitalisation in late infancy	Haemoglobin electrophoresis: HbF≥85% HbA=8, HbA2=7%.	Presence of HbA, rules out β-thalassaemia major variant. Laboratory parameters suggestive of thalassaemia. Raised HbA2 levels may correlate to an intermedia form. Further iron testing deferred by parents due to financial constraints.	Child was transfused at 10 mL/kg to bring Hb to 10.1 g/dL. Post hospitalisation frequency: 2 transfusions annually.
	Haematological parameters:Hb=7.3 g/dL. MCV=73.9 fL, MCHC=27.1 pg.		
	Peripheral smear: 90% observed RCCs normocytic normochromic, 10% microcytes and reticulocytes.		
	Clinical features: hepatosplenomegaly+second-degree consanguinity.		
	No antenatal history, live birth at home. Non-vaccinated.		Child was vaccinated as per the ICMR schedule.
Hospitalisations when the patient was a preschooler and schooler (three hospitalisations)	Haemoglobin electrophoresis: HbF≤1% HbA=92.4%, HbA2=6.8%.	Raised HbA2 levels. Repeat samples, show similar parameters.	Laboratory and clinical features suggestive of β-thalassaemia intermedia.
	Haematological parameters:Hb=8.3 g/dL. MCV=75.2 fL, MCHC=30.3 pg.	Anaemia noted, suggested for blood transfusions. Iron studies deferred in all three hospitalisations.	Increased frequency of transfusions as per age scaling. Normal growth curves, improbable iron deficiency.
	Peripheral smear: 80% observed RCCs normocytic normochromic, 15% microcytic normochromic, 5% reticulocytes.		
	Clinical features: hepatosplenomegaly+jaundice.	Suggested splenectomy in view of β-thalassaemia, patient's parents refused surgical intervention.	Regular outpatient visits scheduled for blood transfusions. Post-hospitalisation frequency: 4 transfusions annually.

Hb, haemoglobin; HbA2, haemoglobin comprising alpha and gamma chains; HbA, adult haemoglobin; HbF, fetal haemoglobin; ICMR, Indian Council of Medical Research; MCH, mean corpuscle haemoglobin; MCHC, mean corpuscular haemoglobin concentration; MCV, mean corpuscle volume; RCC, red cell count.

multinucleated erythroblasts were also seen. Prominent features of marked erythroid hyperplasia, with a myeloid to erythroid ratio of 1:15, were also noted (figure 2). Bone marrow biopsy findings were used in aid with Hams test to confirm the diagnosis. Further efforts were made, to disaffirm other causes of dyserythropoiesis as shown in table 3.

DIFFERENTIAL DIAGNOSIS

Based on the presentation in lieu of missed blood transfusions, the current symptom profile was attributed to severe anaemia. The negative hepatitis panel, normal reticulocyte counts and complete blood counts with a Mentzer index (mean corpuscle volume÷red cell count) of 24.9 led to uncertainty regarding the initial β-thalassaemia intermedia diagnosis.[5–7] At the current admission, the patient had an HbA2 levels of 4.3% (elevated). The diagnosis made during the patient's infancy could have been due to the result of unavailability of further confirmatory testing of β-thalassaemia and by relying on the HbA2 levels and suggestive peripheral smear findings.[8] This was further disaffirmed by a negative β-thalassaemia mutation analysis (using PCR). The raised HbA2 levels could have been a physiological response to erythropoietic stress. Raised lactase dehydrogenase (LDH) levels with the CT of the abdomen showing multiple heterogeneous liver nodules raised concerns for hepatocellular carcinoma, which was ruled out on the basis of benign FNAC findings and normal serum alpha-fetoprotein values. Based on the low haemoglobin, low platelet count, low white cell count (WCC) (pancytopenia) and disproportionate reticulocyte count, a wider differential included acute myeloid leukaemia, lymphoma and progenitor cell dyserythropoietic conditions such as red cell aplasia. A negative G6PD screen and Coombs testing helped to rule out other causes of intravascular haemolysis.

TREATMENT

The patient was transfused with eight units of whole blood over 3 days, abiding by the massive transfusion protocol.[9] Following blood product transfusions, the haemoglobin was brought up to 9.1 g/dL. Low-dose furosemide was given to maintain a euvolaemic state. The patient's calcium was adequately monitored after each transfusion and was supplemented with 4 g of calcium gluconate over the entire process. One month post the emergency admission, following the resolution of the ascites, the patient was taken up for splenectomy after obtaining necessary consent.

OUTCOME AND FOLLOW-UP

The patient was splenectomised with no intraoperative and postoperative complications. At the 1-year follow-up appointment, raised serum ferritin levels (1137 ng/mL) were noted and the patient was started on tablet deferasirox at 20 mg/kg. At the 2-year period, adequate control of the serum ferritin levels was achieved (1137 to 255 ng/mL). Postsplenectomy, the frequency of blood transfusions have reduced to 1–2 units per year.

DISCUSSION

The CDAs are a rare group of hereditary hypoproliferative anaemias. Genetic studies have shown that most mutations in CDAs occur at the gene locus 20p11 (CDAN2). Defects at this locus are mostly associated with the type II variant.[1 10 11]

Table 2 Summary of investigations

Investigations	Results	Reference range
Haemoglobin	3.8 g/dL	11.5–16.5 g/dL (females)
Red cell counts	3.0×10^{12}/L	$3.8–5.8\times10^{12}$/L (females)
WCCs	1.9×10^{9}/L	$4–11\times10^{9}$/L
Platelets	106×10^{9}/L	$150–400\times10^{9}$/L
MCV	74.9 fL	77–93 fL
MCH	28.8 pg	27–32 pg
MCHC	25.2 g/dL	30–35 g/dL
Haematocrit	21.20%	37%–47% (females)
Reticulocyte count	4.10%	(Uncorrected value)
Corrected reticulocyte count (reticulocyte % × (patient haematocrit/normal haematocrit))	2% (normal)	0.5%–2.5%
Peripheral smear	Normocytic normochromic anaemia with few microcytes.	
HIV, hepatitis screening	Non-reactive with no serum immunoglobulins for hepatitis A, B and E.	
Total bilirubin	3.8 mg/dL	0.3–1.3 mg/dL
Direct bilirubin	1.0 mg/dL	0.1–0.4 mg/dL
Indirect bilirubin	2.8 mg/dL	0.2–0.4 mg/dL
Total protein	5.8 g/dL	6.7–8.6 g/dL
Serum albumin	2.2 g/dL	3.5–5.5 g/dL
SGOT	31 U/L	12–38 U/L
SGPT	24 U/L	7–41 U/L
GGT	15 IU/L	9–58 IU/L
LDH	759 U/L	115–221 U/L
PT-INR	1.19	1
Iron profile	Showed raised serum ferritin—895 ng/mL. Rest of iron profile was within normal limits.	Ferritin—10–150 ng/mL (females)
Indirect Coombs test	Did not show haemolysis.	
HPLC (haemoglobin electrophoresis)	HbF≥0.1%, HbA=95.6% HbA2=4.3% (raised)	
Serum electrolytes (Na, K, Ca, Bicarb.)	All within normal limits	
Serum-ascites albumin gradient	2.1 (transudative picture)	
β-thalassaemia mutation analysis	Negative for homozygous and carrier state.	
Intravascular haemolysis panel	Low haptoglobin (4.0 mg/dL). Normal G6PD enzyme levels. Indirect Coombs showed no haemolysis. Increased osmotic fragility noted.	Haptoglobin=60–270 mg/dL
Radiological and pathological studies		
Ultrasound abdomen	Splenomegaly with ascites. Two hypoechoic lesions within the liver with mild bilateral pleural effusions.	
CT-abdomen (with contrast)	Enhancing lesions in right lobe of liver	
Ascitic fluid CBNAAT	Negative	
Ascitic fluid cytology	Negative for malignant cells. Normal cell distribution.	
Alpha-fetoprotein levels	6.39 ng/mL	
Fine-needle biopsy of liver lesions (two specimens from two sites)	Regenerative nodules.	
Bone marrow biopsy	Showed multiple erythroblasts in the same phase of arrested development. Thirty per cent of erythroblasts present in binucleate form. Few cells with marked karyorrhexis noted. Findings suggestive for dyserythropoietic anaemia type II.	
Hams test	Positive for haemolysis in acidified serum.	

CBNAAT, cartridge-based nucleic acid amplification; GGT, gamma-glutamyl transferase; HPLC, high-performance liquid chromatography; LDH, lactase dehydrogenase; MCH, mean corpuscle haemoglobin; MCHC, mean corpuscular haemoglobin concentration; MCV, mean corpuscle volume; PT-INR, prothrombin/international normalised ratio; SGOT, serum glutamic-oxaloacetic transaminase; SGPT, serum glutamic pyruvic transaminase; WCC, white cell count.

This gene locus at CDAN2 codes for the cytoplasmic coat protein II complex- SEC23B, which regulates intracellular trafficking. In addition to regulating intracellular transport, mutations in SEC23B could cause errors in cytokinesis, which could explain why marrow biopsy findings show erythroblasts arrested at the same phase of development (figure 2).[1 10 11]

Majority of the patients (80% of affected pool) are asymptomatic and do not require regular transfusions.[1] Although second-degree consanguinity was noted in our patient, the patient's parents, relatives and grandparents denied the history of any familial blood disorders. The lack of available family medical history was considered to be due to the disease being asymptomatic in this group.[1 8] Clinical features in active presentations could present with histories of long-standing of anaemia dating back to childhood, with supportive laboratory investigations showing indirect hyperbilirubinaemia, normal to mildly elevated reticulocyte count, low to normal haptoglobin levels and raised LDH levels.[1 3] Peripheral smear findings may show normocytic anaemia, basophilic stippling and anisopoikilocytosis.[1]

Patients with CDA have been mistakenly diagnosed with congenital anaemias such as hereditary spherocytosis.[1 3 4] In our case, CDA was mistaken as β-thalassaemia, as such a diagnosis in countries with low medical infrastructure are often presumptive and are made by heavily relying on the HbA2 levels, suggestive clinical findings (anaemia and hepatosplenomegaly) and history of consanguinity within the family. The delay in diagnosis herein was due to socioeconomic factors directly impacting patient care and the presumptive diagnosis in the presence of mimicking

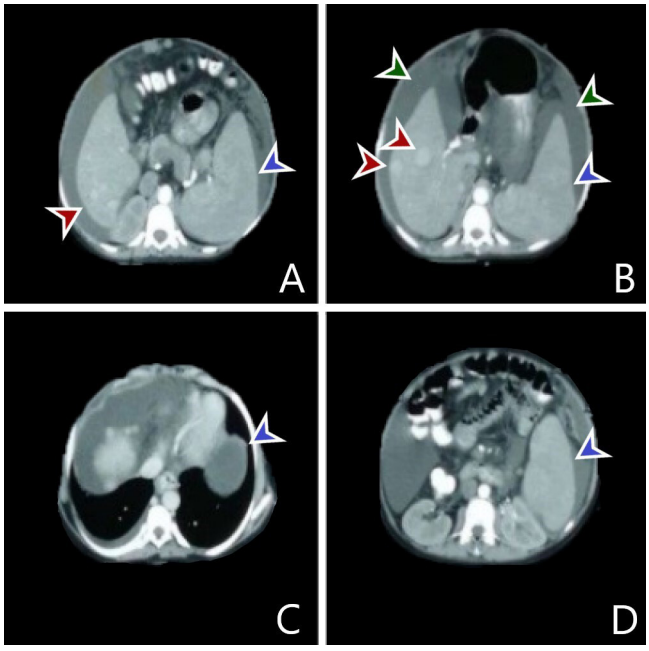

Figure 1 Contrast CT sections of the abdomen. Gross ascites (marked in green), multiple liver opacities (marked in red) and massive splenomegaly (marked in blue).

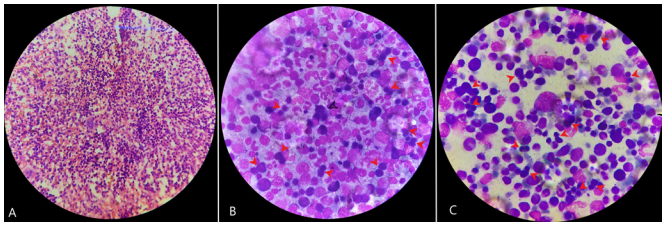

Figure 2 Bone marrow trephine histopathological sample (H&E stain) demonstrating. (A) Erythroblast hyperplasia (×10). (B) Multiple binucleate erythrocytes comprising 30% of the total viewed erythroblasts (marked in red) along with a cell with noted karryohexis (marked in black) (×100). (C) Multiple binucleate erythrocytes (marked in red) (×100).

Table 3 Investigative history and profile for ruling out secondary dyserythropoiesis

Conditions causing secondary dyserythropoiesis	History and investigations carried out for patient in case
Preterm birth	Patient was a full-term vaginal delivery with no neonatal complications.
Severe iron-deficiency anaemia	Showed raised serum ferritin—895 ng/mL. Rest of iron profile was within normal limits.
B_{12} deficiency	MCV was on the lower limit, no neurological sequelae noted. Patient was a non-vegetarian and reported adequate meat consumption.
Severe malnutrition	Growth curves were adequate, normal calorie intake, no stunting noted.
Medication adverse side effects (eg, zidovudine)	Not on any medications.
Chronic alcohol intoxication	Normal liver function tests, denies history.
HIV infection	Negative on ELISA for HIV-1 and HIV-2.
Hereditary infantile pyropoikilocytosis (HIP)	Patient had a normal corrected reticulocyte count. Children with HIP often have marked reticulocytosis.
Congenital bronchopathy	Small pleural effusions were due to anaemic failure. No history or complains of respiratory infections or cough since childhood. Normal respiratory examination.
Congenital cardiopathy	Normal ECG and two-dimensional echo. No history or complaints of palpitations or chest pain.

MCV, mean corpuscle volume.

Patient's perspective

'I used to feel very exhausted and run down all the time. I thought I had thalassemia since I was young, but it turned out to be something else. After undergoing surgery, I have noticed a significant improvement in my energy levels and need fewer blood transfusions.'

Learning points

- The congenital dyserythropoietic anaemias (CDAs) are a group of rare hereditary hypoproliferative anaemias with type II as its most noted form.
- Patients with CDA type II may have pallor and hepatosplenomegaly with peripheral smear studies showing varying degrees of normocytic anaemia with normal to mildly raised reticulocyte counts.
- Due to the rarity of CDA, patients have been mistaken to have other congenital forms of anaemia, hence clinical suspicion may arise with disproportionate reticulocyte counts to the severity of anaemia.
- Trephine bone marrow biopsies may show numerous binucleate erythroblasts with marked erythroid hyperplasia with occasional erythroblasts with karryohexis.
- Splenectomy in transfusion dependent patients may be beneficial in reducing the frequency of transfusions.

laboratory values. A positive Hams test, and the feature of binucleate erythroblasts, as seen in figure 2, comprising more than 30% of erythroblasts in binucleate forms were in itself highly indicative of CDA type II. The low platelet count and WCC in our patient could have been attributed to the selective expansion of red blood cell progenitors in the bone marrow, in response to chronic and severe anaemia. To diagnose CDA type II accurately, it is important to eliminate secondary causes of dyserythropoiesis. This is because, similar bone marrow biopsy findings can be seen in both CDA type II and other causes of dyserythropoiesis.[1 5] In standard practice, along with the gold-standard investigation of bone marrow examination, confirmation can be achieved through Hams test or Oxford Red Cell Gene Panel testing or Red Cell Membrane electrophoresis.[5] The patient's family could not afford genetic testing. Red cell membrane electrophoresis was not available at our centre.

Treatment revolves around early identification of the disease through clinical signs and laboratory testing. Studies have shown that hyperferritinaemia seen particularly in CDA type II, could be an outcome of increased erythroid precursor regulators (growth differentiation factor 15) reducing the expression of hepcidin in iron metabolism causing secondary haemochromatosis.[1 12 13] In this case, it was not possible to distinguish between the hyperferritinaemia seen in CDA and the unchelated long-term blood transfusions. Our patient was given tablet deferasirox at a dosage of 20 mg/kg at the 1-year follow-up period, when her ferritin levels were found to be above 1000 ng/mL.[14] The role of splenectomy has been controversial in the treatment of CDA type II in mild to moderate anaemia states. However, in transfusion-dependent states with massive splenomegaly, splenectomy could help in reducing the frequency of transfusions. In our case, postsplenectomy, the number of transfusions decreased from 6 per year to 1–2 per year.[1 3 14 15] In patients who do not respond to splenectomy, bone marrow transplantation has shown promising benefits.[14 16] Homologous grafts from the family members are discouraged in such conditions due to the familial nature of the disease, hence relying on extra-familial matched donors.

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Case reports provide a valuable learning resource for the scientific community and can indicate areas of interest for future research. They should not be used in isolation to guide treatment choices or public health policy.

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REFERENCES

1 Iolascon A, Heimpel H, Wahlin A, *et al*. Congenital dyserythropoietic anemias: molecular insights and diagnostic approach. *Blood* 2013;122:2162–6.
2 Heimpel H, Anselstetter V, Chrobak L, *et al*. Congenital dyserythropoietic anemia type II: epidemiology, clinical appearance, and prognosis based on long-term observation. *Blood* 2003;102:4576–81.
3 Tandon B, Peterson LC, Norwood S, *et al*. Congenital dyserythropoietic anemia type II (CdA II) diagnosed in an adult patient. *J Hematopathol* 2010;3:149–53.

4 Kedar P, Parmar V, Devendra R, *et al*. Congenital dyserythropoietic anemia type II mimicking hereditary spherocytosis in Indian patient with SEC23B-Y462C mutations. *Ann Hematol* 2017;96:2135–9.
5 Heimpel H, Kellermann K, Neuschwander N, *et al*. The morphological diagnosis of congenital dyserythropoietic anemia: results of a quantitative analysis of peripheral blood and bone marrow cells. *Haematologica* 2010;95:1034–6.
6 Russo R, Andolfo I, Manna F, *et al*. Multi-Gene panel testing improves diagnosis and management of patients with hereditary anemias. *Am J Hematol* 2018;93:672–82.
7 Heimpel H. Congenital dyserythropoietic anemias: epidemiology, clinical significance, and progress in understanding their pathogenesis. *Ann Hematol* 2004;83:613–21.
8 Hershko C, Izak G. Pathophysiology of blood disorders-red-cell disorders. papers presented at 2nd meeting of mediterranean blood club and meeting of israeli society of hematology and blood-transfusion. *Isr J Med Sci* 1978;14.
9 Patil V, Shetmahajan M. Massive transfusion and massive transfusion protocol. *Indian J Anaesth* 2014;58:590–5.
10 Iolascon A, Esposito MR, Russo R. Clinical aspects and pathogenesis of congenital dyserythropoietic anemias: from morphology to molecular approach. *Haematologica* 2012;97:1786–94.
11 Fukuda MN. Congenital dyserythropoietic anaemia type II (HEMPAS) and its molecular basis. *Baillieres Clin Haematol* 1993;6:493–511.
12 Tamura H, Matsumoto G, Itakura Y, *et al*. A case of congenital dyserythropoietic anemia type II associated with hemochromatosis. *Intern Med* 1992;31:380–4.
13 Bird AR, Jacobs P, Moores P. Congenital dyserythropoietic anaemia (type II) presenting with haemosiderosis. *Acta Haematol* 1987;78:33–6.
14 Marwaha RK, Bansal D, Trehan A, *et al*. Congenital dyserythropoietic anemia: clinical and hematological profile. *Indian Pediatr* 2003;40:551–5.
15 Vassiliadis T, Garipidou V, Perifanis V, *et al*. A case of successful management with splenectomy of intractable ascites due to congenital dyserythropoietic anemia type II-induced cirrhosis. *World J Gastroenterol* 2006;12:818–21.
16 Iolascon A, Sabato V, de Mattia D, *et al*. Bone marrow transplantation in a case of severe, type II congenital dyserythropoietic anaemia (CdA II). *Bone Marrow Transplant* 2001;27:213–5.