Rare disease

Congenital dyserythropoietic anaemia type II: a rare entity

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Summary

Congenital dyserythropoietic anaemias (CDAs) are a group of rare hereditary disorder characterised by ineffective erythropoiesis and dyserythropoiesis. Among the three variants, type II is the most common. The authors are presenting two cases of CDA type II in two sisters.

BACKGROUND

Congenital dyserythropoietic anaemia (CDA) is an extremely rare disease.

CASE PRESENTATION

Case 1

A 4-year-old female presented to paediatric OPD with complaints of progressive pallor and easy fatigability. General examination showed moderate pallor. Hepatosplenomegaly was seen on systemic examination.

Investigations showed haemogram – hemoglobin (Hb) -5.5 gm%, total lymphocyte count (TLC) - 5100 cells/mm³.

Differential leucocyte count (DLC) – p₅₅l₂₇immature cells₁₈ (promyelocyte-01, myelocyte-12, metamyelocyte-05).

General blood picture revealed moderate to severely hypochromic red blood cells (RBCs) showing marked anisopoikilocytosis. Macrocytes along with few microcytes, tear drop cells, pencil cells and elliptocytes were seen. Nucleated RBCs were 36/100 white cell count (WCC). Few erythroblasts were bi and multinucleated and mitosis was also noticed in peripheral blood (figure 1). Reticulocyte count was 0.5%.

Bone marrow aspiration showed erythroid hyperplasia with reversal of myeloid:erythroid ratio(1:2). Bi and multinucleated erythroblasts were present some showing abnormal mitosis. Features of dyserythropoiesis, karyorrhexis and nucleocytoplasmic asynchrony were also seen (figure 2). Cells of myeloid series and megakaryocytes were unremarkable.

Figure 1 Blood smear from a patient with CDA II showing mitosis (A), bi and multinucleation (B–D).

Figure 2 Bone marrow smear from a patient with CDA type II. Marked erythroid hyperplasia with mitosis (A) binuclearity and multinuclearity especially of late erythroblasts (B, C) and cytoplasmic blebbing (D).

Figure 3 Blood smear from a patient with CDA type II showing bi and multinucleation (A, C, D) and mitosis (B).

Figure 4 Bone marrow smear from a patient with CDA type II showing marked erythroid hyperplasia along with binuclearity and multinuclearity especially of late erythroblasts (A, B) and mitosis (C).

Serum bilirubin was 3 mg% (Direct fraction - 0.3 mg% and indirect fraction - 2.7 mg%).

A differential diagnosis of iron deficiency anaemia, megaloblastic anaemia, haemolytic anaemia and congenital dyserythropoietic anaemia was made.

Iron profile, Vitamin B₁₂ and Folic acid levels and Coomb's test were unremarkable.

Serum haptoglobin level was reduced, lactate dehydrogenase level was raised.

Ham test was found to be positive and electrophoresis of erythrocyte membrane proteins showed narrow band 3 and CD₅₅ and CD₅₉ were negative.

On the basis of above investigations a diagnosis of CDA type II was rendered.

Case 2

A 7-year-old female, elder sister of above mentioned case presented with similar complaints.

General examination revealed severe pallor and hepatosplenomegaly was seen in systemic examination.

On investigations haemogram showed Hb- 4 gm%, TLC- 15 000 cells/mm³.

DLC- P₇₃L₂₀ Immature cells₀₇ (promyelocyte-01, myelocyte-04, metamyelocyte-02).

Peripheral blood film showed severely hypochromic RBCs along with marked anisopoikilocytosis. Many macrocytes, microcytes, ovalocytes, macro-ovalocytes, tear drop cells and target cells seen. Non-specific findings like basophilic stippling and cabot's ring were also noticed. Nucleated RBCs were 125/100 WCC. Features of dyserythropoiesis in the form of bi and multinucleated erythroblasts were observed (figure 3).

Bone marrow examination showed increased cellularity and erythroid hyperplasia. Reversal of myeloid: erythroid ratio (1:3) was noticed. Erythroblasts showed features of dyserythropoiesis in the form of bi and multinuclearity, dumbbell-shaped nucleus with internuclear bridging, nucleocytoplasmic asynchrony and karyorrhexis (figure 4). Megakaryocyte and myeloid series cells were unremarkable.

Unconjugated bilirubin was raised.

This patient was also investigated on the similar lines and similar results were noticed and a diagnosis of congenital dyserythropoietic type II was made and both the patients were referred to higher centre.

DISCUSSION

CDAs are a group of rare genetic disorders characterised by ineffective erythropoiesis and dyserythropoiesis.^{1 2}

On the basis of morphology and serological tests CDA can be classified in to three major types, type I, II and III.³⁻⁵ Of the three subtypes, type II CDA is most common which accounts for two-third of all cases followed by CDA type I which has an autosomal recessive inheritance. It is assumed that abnormal nucleoprotein synthesis in the form of abnormal nuclear histone proteins is responsible for abnormal mitosis.^{6 7} CDA type III is uncommon and maximum number of cases has been reported in single large Swedish family whereby the mode of inheritance was autosomal dominant. In addition to original classification, CDA type IV is also described which shows typical morphological features of CDA type II but negative acidified serum test.⁸

The term type II CDA was first coined by Heimpel and Wendt¹ in 1968. Among all the three subtypes CDA type II

is the most common. It is inherited as autosomal recessive. In addition to morphological abnormalities type II CDA have some serological abnormalities. It is also known as HEMPAS (hereditary erythroblastic multinuclearity with a positive acidified serum test).² Acidified serum test is also positive in paroxysmal nocturnal haemoglobinuria (PNH). Sucrose lysis test is useful in differentiating these two conditions as this test is positive in PNH and negative in CDA type II. Positive CD₅₅ and CD₅₉ are diagnostic of PNH.

CDA can be placed in differential diagnosis in a patient presenting with congenital anaemia with indirect hyperbilirubinemia, low reticulocyte count and low or absent plasma haptoglobin. In most of the cases patients present with long history of anaemia and/or hyperbilirubinemia.⁹ Anaemia may range from mild to such a severe degree as may require repeated blood transfusions.⁹ Peripheral blood smear shows non-specific findings like variable degrees of hypochromia, anisopoikilocytosis and basophilic stippling. However binucleated normoblast can also be seen in peripheral smear. Bone marrow examination is very helpful in making a diagnosis of CDA as it may show erythroid hyperplasia and bi and multinuclearity of erythroid precursor cells. Electrophoresis of erythrocyte membrane protein by sodium dodecyl sulphate polyacrylamide gel shows abnormal band three protein.¹¹ This abnormal band three protein is hydrophobic which tends to cluster and causes disruption of cytoskeleton, thereby resulting in abnormal membrane architecture.

Splenomegaly is present in almost all the cases of CDA and its absence rules out the possibility of CDA. Cholelithiasis and iron overload are the complications that result due to ineffective erythropoiesis. Iron overload is responsible for deposition of iron in liver, heart and pancreas.

Differential diagnosis includes megaloblastic anaemia, β thalassaemia, sideroblastic anaemia, myelodysplasia and erythroleukemia. These diseases can be differentiated from CDA by bone marrow examination and acidified serum test.

Treatment includes splenectomy in patients requiring repeated blood transfusions. Patients should be routinely monitored for iron overload because it can occur even in absence of repeated blood transfusions.¹² Iron chelation therapy and phlebotomy is used when iron overload

is present. Allogenic bone marrow transplantation was reported to be curative in one case.¹³

Learning points

- ▶ Acidified serum test is helpful in making a diagnosis of CDA.
- ▶ Acidified serum test is positive in PNH.
- ▶ Iron overload is common in patients of CDA.

Competing interests None.

Patient consent Obtained.

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