Case study

Congenital Dyserythropoietic Anaemia Type II: A Rare Blood Disorder in a Nigerian Child

ABSTRACT

The congenital dyserythropoietic anaemias (CDA) are a rare group of inherited haematological disorders characterized by congenital anaemia, ineffective erythropoiesis in the bone marrow and dysplasia in developing erythroblasts. In Africa where sickle cell anaemia and thalassaemias are common, diagnosis of CDA may be missed. We report a six year old girl who presented in anaemic heart failure with a haemoglobin concentration of 5.1g/dL and a history of recurrent anaemia of two years duration which required multiple blood transfusions. Peripheral blood film features showed red cell anisopoikilocytosis with occasional nucleated red cells- some of which were multinucleated. Her haemoglobin genotype was AA. Bone marrow aspiration revealed a markedly hypercellular marrow with severe erythroid hyperplasia and dyserythropoiesis. Her serum ferritin was also markedly elevated. Based on the clinical, laboratory and characteristic bone marrow findings, a diagnosis of CDA type II was made. She was transfused and placed on iron chelation therapy. Her parents were counseled on treatment options and she is currently on follow up.

Keywords: Congenital dyserythropoietic anaemia, CDA, dyserythropoiesis, dysplasia, anaemia, inherited anaemias

1. INTRODUCTION

The congenital dyserythropoietic anaemias (CDA) are a rare group of inherited haematological disorders characterized by congenital haemolytic anaemia, massive ineffective erythropoiesis in the bone marrow associated with distinct dysplasia of the erythroblasts (dyserythropoiesis) and subsequent development of secondary iron

overload. Patients with CDA usually present clinically in early life with anaemia, jaundice, splenomegaly, and have a suboptimal reticulocyte response for the degree of anaemia highlighting the associated ineffective erythropoiesis. The peripheral blood film in CDA commonly shows anisopoikilocytosis of the red cells, with basophilic stippling while the leukocytes and platelets have normal morphology. Nucleated red cells may be seen on the peripheral smear. The bone marrow aspirate in CDA is essential in diagnosis and differentiates this disease into 3 distinct types morphologically while certain types of CDA have specific genetic mutations associated with them.

Type I CDA is inherited in an autosomal recessive fashion. Bone marrow erythropoiesis is megaloblastic with presence of multinucleated erythroblasts and the distinct inter-nuclear bridges between erythroblasts seen in 0.6% –7.9% of total erythroblasts.[1,2] Electron microscopy shows spongy appearance of the heterochromatin in more than half of the erythroblasts with enlarged nuclear pores and invagination of cytoplasm including some cytoplasmic organelles into the nucleus.[3] Due to increased iron absorption, with increasing age there is secondary haemochromatosis irrespective of blood transfusion. Mutations in the *CDAN1* and C15ORF41 genes on chromosome 15 have been associated with most cases of type I CDA.[1] Interferon therapy increases haemoglobin concentration and reduces iron overload in majority of CDA I cases.

Type II is the most common form of CDA, the red cells are lysed by acidified serum therefore the disease is also known as hereditary erythroblastic multinuclearity with positive acidified serum lysis test (HEMPAS). Like CDA I, inheritance is autosomal recessive and anaemia ranges from none to severe. Patients with CDA II also have jaundice and splenomegaly. The bone marrow shows binuclearity in 10-50% of the total erythroblasts. Up to 15% of cases are transfusion dependent.[4] Secondary haemochromatosis is usually present in affected persons more than twenty years of age. Mutations in the SEC23B gene on the short arm of chromosome 20 involved in vesicle trafficking from the endoplasmic reticulum to the Golgi apparatus have been implicated in the aetiology of CDA II.[5]

Congenital dyserythropoietic anaemia type III has been reported as being inherited in an autosomal dominant manner in several families with mutations of the CDAN3 gene (also of unknown function) on chromosome 15. However, fewer sporadic cases with autosomal recessive inheritance have been reported and they appear to have a different genetic mutation from CDAN3. The CDA3 gene is also expressed in B-lymphocytes and retinal cells.[6] This type of CDA is the rarest form with only about 60 cases reported worldwide. The anaemia in CDA III tends to be mild to moderate and not usually requiring transfusions while splenomegaly is usually absent. It has distinct bone marrow morphology consisting of giant erythroblasts with multiple nuclei, sometimes up to ten in number. This form of CDA has been associated with a predisposition to retinal detachment and development of lymphomas, monoclonal gammopathy of undetermined significance and myeloma.[7,8]

Other even rarer forms of CDA which do not fit into the above three have been described and classified as CDA IV – VII.[9] Therapeutic options in CDA include the use of interferon-α (only effective in type I), splenectomy, iron chelation and allogeneic haemopoietic stem cell transplantation.[10]

We report a six year old female with recurrent anaemia, jaundice, hepatosplenomegaly and multiple transfusions in whom the diagnosis of CDA II was made.

2. CASE REPORT

A six year old girl presented at the paediatric clinic with features of extreme weakness, pallor and breathlessness. She had a two year history of recurrent anaemia which required regular blood transfusions usually every three months, she had already been transfused with more than ten units of blood over time. There was also a history of persistent jaundice and passage of coke-coloured urine. She was not a known sickle cell anaemia or thalassaemia patient (her mother reported her Haemoglobin genotype to be AA), neither was there a family history of sickle cell and thalassaemia. She was

the first child of her mother who had an uneventful prenatal period while pregnant, with normal vaginal delivery (birth weight 3.5kg) and uneventful post partum period. During her neonatal life, there was no history of jaundice, neither was there any history of parents with consanguineous marriage, or a similar illness in any family member, including her younger sibling.

On examination at presentation, she was acutely ill-looking, extremely weak but conscious. She was small for age with a weight of 15kg (below the 3rd percentile), height 104cm (below the 3rd percentile), frontal bossing and gnathopathy. She was severely pale, moderately icteric and afebrile with a temperature of 37.4^0C. There was tachypnoea with a respiratory rate of 52cycles per min, and obvious respiratory distress with flaring alae nasi and subcostal recession. On auscultation her chest was clinically clear. The heart rate was 140 beats per minute, with a blood pressure of 100/50mmHg and the presence of a haemic murmur There was no peripheral lymphadenopathy and examination of the abdomen revealed tender hepatomegaly of 6cm and non-tender splenomegaly of 5cm both below the costal margin.

A working clinical diagnosis of recurrent severe haemolytic anaemia in heart failure secondary to haemoglobinopathy (to rule out lymphoproliferative disorder) was entertained. She was admitted, placed on oxygen and transfused with sedimented red cells. Laboratory investigations done included a full blood count which revealed severe anaemia with a haematocrit of 15%, haemoglobin concentration of 5.1g/dL and normal red cell indices. Total white cell count was 9.4 X 10^9/L and platelet count was 231 X 10^9/L. Her reticulocyte count was 2.9%, corrected reticulocyte count was 0.97 while the reticulocyte production index was 0.39. Her haemoglobin (Hb) genotype was AA and the mother gave a history of having done the Hb genotype several times before with the same result. Both direct and indirect antiglobulin tests were negative. Liver functions

tests showed normal enzymes and proteins values, but a high total bilirubin of 104µmol/L and conjugated bilirubin of 17.4mmol/L. Serum uric acid was 299µmol/L. She was seronegative for HIV, hepatitis B and C viruses. Urinalysis done was positive for blood cells, urobilinogen and bilirubin with a urine pH of 8.0. Urine microscopy showed granular, epithelial and red blood cell casts. Glucose 6 phosphate dehydrogenase assay was normal at 12.5 µ/Hb.

On the third day her clinical condition was stable and she was discharged home. However she was brought back to the hospital about 3 months later for similar symptoms. Urgent haematocrit this time was 18%. Peripheral blood film requested for revealed marked anisopoikilocytosis, some macrocytes, tear drop cells, few polychromatic cells, basophilic stippling, fragmented red cells and presence of several nucleated red cells- some of which were multinucleated (Fig 1). A repeat Hb genotype using HPLC showed low HbA (74.1%) with markedly increased Hb F (23.8%) and HbA2 of 2.1%. Bone marrow aspiration was done and showed a markedly hypercellular marrow, severe erythroid hyperplasia with a reversed myeloid/erythroid ratio of 1:2, dyserythropoiesis with erythroid multinuclearity in >10% of late erythroid precursors and significant karyorrhexis. Myelopoiesis and megakaryopoiesis were essentially normal (Fig 2). Serum ferritin was markedly elevated (2,658ng/ml). In the absence of availability of electron microscopy or molecular studies (unavailable in our locality), a diagnosis of congenital dyserythropoietic anaemia (type II) was made based on clinical and laboratory findings with characteristic bone marrow findings. She was transfused once again and placed on iron chelation therapy. Her parents were counseled on the disorder and therapeutic options including splenectomy and haematopoietic stem cell transplantation.

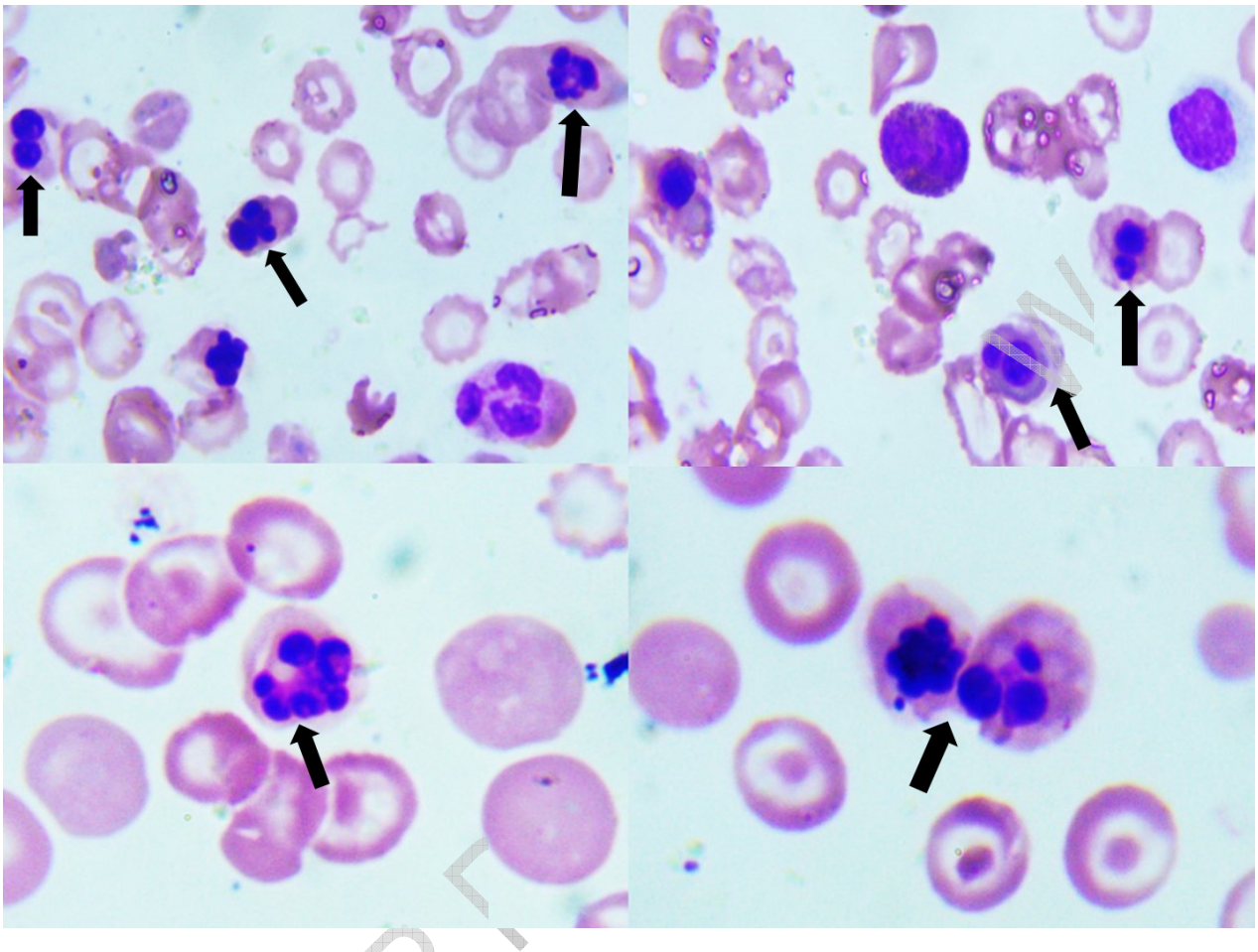

Fig.1 – Peripheral blood film showing presence of several nucleated red cells that are bi- and multi-nucleated (arrows).

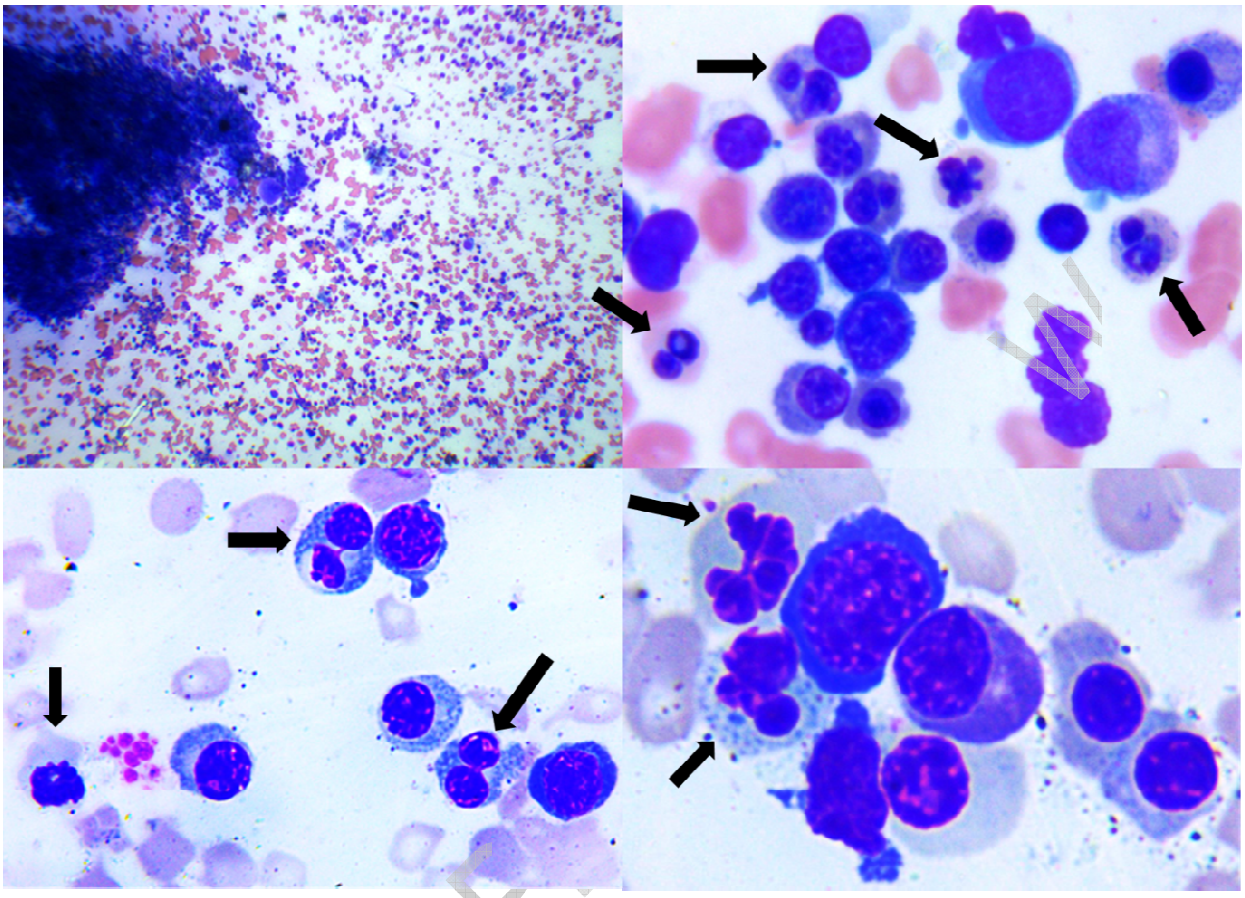

Fig.2- Bone Marrow Aspiration- arrows pointing to abnormal erythroblasts with multiple nuclei (some are bi-nucleated while others are multiple, resembling a bunch of grapes).

3. DISCUSSION

The congenital dyserythropoietic anaemias are a rare group of inherited haemolytic anaemias with characteristic bone marrow morphologic findings both on light and electron microscopy which is the basis of classification of CDA into specific subtypes.[11] The diagnosis is usually made in childhood (but may also be diagnosed for the first time in adults).[12] Our patient was six years old. In our environment where haemoglobinopathy is common, a child presenting with recurrent anaemia requiring transfusions, with jaundice, hepatsplenomegaly, frontal bossing and gnatopathy would easily be diagnosed as having sickle cell anaemia.[13] However, our patient's genotype

had been done severally which ruled out any form of sickle cell disease or thalassaemia, she also did not have other inherited haemolytic anaemias or an immune cause of the anaemia which warranted a bone marrow aspirate (BMA) to be done. In sickle cell anaemia and most other haemolytic anaemias, there is reticulocytosis. However, due to ineffective erythropoiesis ongoing in the marrow in CDA the reticulocyte count (even if there is reticulocytosis), will be inadequate for the degree of anaemia.

The peripheral blood film (PBF) although not diagnostic, can be used to rule out sickle cell anaemia, thalassaemia, red cell membrane disorders or G-6-PD deficiency. In the index case, the PBF not only ruled out these diseases but also showed presence of several multinucleated erythroblasts. The BMA remains a very important diagnostic investigation in anaemia of unknown cause and is essential in the diagnosis of CDA where the characteristic erythroblasts are seen. Although the facility for genetic studies to detect the presence of mutations in the SEC23B gene[4, 10] were unavailable, the characteristic BMA findings of erythroid hyperplasia, binucleated and multinucleated erythroblasts, karryrhexis and basophilic stippling were all present.[9]

Due to massive ineffective erythropoiesis and multiple transfusions, serum ferritin is usually high[14] and they require iron chelation therapy as seen in the index case. At the time of presentation to us, our patient had already received over ten units of blood transfusion.

4. CONCLUSION

We conclude that the BMA remains a key diagnostic tool in the diagnosis of anaemia of unknown cause. Although CDA is rare, it must be considered in a child who has recurrent anaemia in whom other causes have been ruled out. Bone marrow examination is essential in identification of the CDAs.

COMPETING INTERESTS

The authors do not have any competing interests to declare.

CONSENT AND ETHICAL APPROVAL

All authors declare that written consent and ethical approval have been collected and preserved by the author.

Conference Disclaimer: - This case was presented as an ABSTRACT in a conference.

Conference name: 2014 Annual Scientific Meeting of the American Society of Haematology.

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