CASE REPORT

A DELAYED DIAGNOSIS OF CONGENITAL DYSERYTHROPOIETIC ANAEMIA IN EARLY ADULTHOOD AFTER YEARS OF TRANSFUSION THERAPY

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Congenital dyserthropoietic anaemias (CDAs) constitute a diverse category of anaemia marked by differing levels of ineffective erythropoiesis and subsequent development of secondary hemochromatosis. Congenital dyserthropoietic anaemia (CDA) type 2 is an uncommon genetic disorder characterized by mild to severe anaemia. The rarity of this condition can contribute to frequent misdiagnoses, as the morphological abnormalities and the clinical features it presents are commonly shared with other anaemias that are clinically related. Therefore, we report a case involving a 24-year-old female patient with complaints of epigastric pain, vomiting, weight loss, and a history of frequent blood transfusions. A bone marrow biopsy confirmed the diagnosis of Congenital Dyserthropoietic Anaemia type 2. The management approach involved interdisciplinary support and regular psychotherapy for both the patient and her family.

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INTRODUCTION

Congenital dyserythropoietic anaemia is an uncommon haematological and congenital condition marked by unique morphological defects in bone marrow erythroblasts and inefficient erythropoiesis.[1] The classification into four types is based on these morphological features, with the initial three types defined by Wendt and Heimpel in 1967. Type I exhibits megaloblastic changes, while Type II, the most prevalent, is marked by normocytic binuclear or multinuclear red cells showing double cytoplasmic membranes under electron microscopy. Type III is identified by significant erythroblastic multinuclearity, forming 'gigantoblasts' with up to 12 nuclei. Type IV is assigned to variants displaying unique characteristics not observed in Types I, II, and III.[2] CDA type 2 typically manifests in early childhood or adolescence, presenting with varying degrees of anaemia. Symptoms may include jaundice, hepatosplenomegaly (enlarged liver and spleen), and the formation of gallstones.[3] In Pakistan, a handful of cases have been reported, and the similarity of symptoms has led to frequent misdiagnoses.[4] The following report focuses on a 24-year-old female who complained of epigastric pain, vomiting, weight loss, and a history of frequent blood transfusions over the past seven years.

CASE PRESENTATION

A 24-year-old woman residing from Okara, was receiving treatment at the Haematology department at CMH, presented to Pakistan Institute of Medical Sciences (PIMS) emergency department on with chief complaints of epigastric pain persisting for the past 3 months. The pain was characterized as dull and non-radiating or postural, was unrelated to food intake. Additionally, she experienced vomiting for the past 20 days, occurring 3–4 times per day and consisting of non-bloody, non-bilious content with food particles. Yellowish sclera was noted for the same duration, and there was no history of burning micturition, flank pain, or bleeding from any site. The patient reported an undocumented weight loss of approximately 3kg over the past 20 days and had undergone cholecystectomy 6 years back.

The patient's vital signs were as follows: blood sugar level of 108 mg/dl, oxygen saturation of 98% in room air, pulse rate of 80 beats per minute, and blood pressure of 110/60 mm Hg. The patient was afebrile. When examined, she showed evidence of anaemia and jaundice. Her cardiopulmonary examination was unremarkable. Glasgow Coma Scale (GCS) was recorded as 15/15. A mild pain in the right upper quadrant was found during the abdominal examination and hepatosplenomegaly. After retaining the patient, a series of baseline investigations were ordered. A full blood panel consisted of Complete Blood Count (CBC), Serum Electrolytes, Liver function tests (LFTs), Renal function tests (RFTs), Direct Comb's Test, Serum Lipase, Serum Amylase, Serum Ferritin, and Serum Lactate Dehydrogenase (LDH) was sent. The labs

revealed normocytic normochromic anaemia with raised red cell distribution width (RDW) on CBC, Hyponatremia on Serum Electrolytes, Raised Alanine Transaminase (ALT), Total, Indirect and Direct Bilirubin on LFTs, and high serum Lipase, while the remaining results were within normal range (Table-1) HB Electrophoresis was carried out since she had not received transfusion in the last 3 months, which was unremarkable.

Abdominopelvic Ultrasound revealed gross Hepatomegaly with altered parenchymal echotexture with mild Splenomegaly and traces of Abdominopelvic ascites. Other causes for hepatosplenomegaly were ruled out through blood cultures and infection screens used for Typhoid, Malaria, Leishmaniasis and Viral hepatitis; however, were all negative.

For further aid in differential diagnosis, a Bone Marrow Biopsy was ordered. The marrow aspiration results showed Hyper cellular fragments and trails with markedly hyperplastic Erythropoiesis showing binuclearity, multinuclearity, dyserythropoiesis and megaloblastic change. (Figure-1)

M:E Ratio was more than 1.Iron was Increased, megakaryocytes were normal and myelopoiesis was active with maturation. Trephine biopsy showed hyper cellular marrow with effaced architecture and an overall cellularity of 80–90%.

Megakaryocytes were found to be normal. Erythropoiesis was hyperplastic with megaloblastic changes. Myelopoiesis was active with maturation. Overall findings were suggestive of congenital dyserythropoietic anaemia CDA Type-II.

Following the confirmation of CDA type II, the patient received symptomatic management throughout her hospitalization. The treatment regimen involved the administration of intravenous fluids such as Dextrose Water, injectable antibiotic Ceftriaxone, injection omeprazole (PPI), injection Domeperidone, injection Aminoleban, Oral Folic Acid Tablets and a transfusion of 1 unit of red cell concentrate.

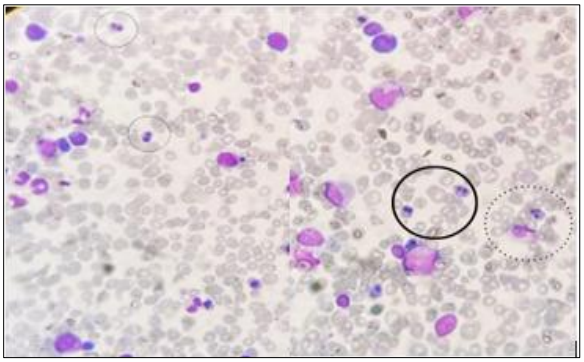

Figure-1

Bone marrow aspirate (Giemsa Stain 1000x) Presence of binucleated erythroblasts (shown in complete circles) Trinucleated erythroblast (shown in dotted circle).

Table-1: Baseline Lab panel of our patient

HB (g/dL)	8.9	12-15	Low
WBC (/µL)	6180	4000-10000	Normal
RBC (million/ µL)	3.15	3.8-4.8	Low
MCV (fL)	83.2	80-98	Normal
MCH (pg)	28.1	27-32	Normal
HCT (%)	26.2	36-46	Low
Platelets (/ µL)	311000	140000-400000	Normal
RDW (%)	20	10-15	High
Neutrophils	68.3	45-70	Normal
Lymphocytes (%)	23.8	20-40	Normal
Direct Coombs test	Negative	Negative	Normal
Ferritin (ng/mL)	287	11-306.8	Normal
Amylase (U/L)	52	20-125	Normal
Lipase (U/L)	44.7	1-38	High
Bilirubin total (mg/dL)	8.3	Upto 0.9	High
Direct Bilirubin (mg/dL)	5.1	0.0-0.3	High
Indirect Bilirubin (mg/dL)	3.2	0.1-0.8	High
ALT-SGPT (U/L)	50.1	4-42	High
Creatinine (mg/dL)	0.452	0.5-1.1	Low
LDH-S (U/L)	141	50-460	Normal
Sodium (mmol/L)	133.5	136-146	Low
Potassium (mmol/L)	3.8	3.5-5.1	Normal

DISCUSSION

A rare haematological disorder known as congenital dyserythropoietic anaemia (CDA) is predominantly found in Central and Western Europe as well as North America. [5]. A wide range of inherited anaemias with anomalies in late-stage erythropoiesis make up CDAs. This causes specific dysplastic alterations in erythroblasts, reticulocytopenia, hypercellularity in bone marrow with inefficient erythropoiesis, refractory anaemia, and the emergence of secondary hemochromatosis. In the differential diagnosis, it is important to differentiate CDA from other illnesses such thalassemia syndromes, certain hemoglobinopathies, congenital myelodysplasia, hereditary sideroblastic anaemia, Black fan-Diamond anaemia, and Fanconi anaemia. Congenital dyserythropoietic anaemias (CDAs) are classified into four types: CDA type 1, CDA type 2, CDA type 3, and CDA type 4.[6] Morphological abnormalities in bone marrow erythroblasts, especially in CDA types I and II, play a crucial role in differentiation. Megaloblastic binucleated erythroblasts, chromatin bridges between nuclei, heterochromatin with a "Swiss-cheese" look, and cytoplasmic invagination into the nucleus are characteristics of CDA type I.[7]

On the other hand, normoblastic binucleated and multinucleated erythroblasts (10–35%) with double plasma membranes at the periphery are the hallmark of CDA type II. Multinucleated erythroblasts with autophagic vacuoles, karyorrhexis, and intranuclear clefts are seen in CDA type III. Similar to CDA types I and II, CDA type IV has dyserythropoietic morphology that includes binucleated erythroblasts and sporadic immature erythroid cells with noticeable heterochromatin.

Diagnosis relies on the investigation of erythrocyte membrane proteins, where the diagnostic hallmark of CDA type 2 is the hypo-glycosylation of band three.[8]

CDA type 2, a rare inherited blood disorder resulting from SEC23B gene mutations, is typically diagnosed in early life and presents with varying degrees of anaemia, jaundice, hepatosplenomegaly, and gallstones.[9] It is the most common among classical CDA types. Recent research links CDA type 2 to Golgi processing disruption in erythroblasts, with chromosome 20's CDAN2 locus implicated in many cases.[10] Diagnosis involves a bone marrow biopsy and the Ham test. Clinically, CDA II individuals exhibit ineffective erythropoiesis, causing hepcidin downregulation, increased iron absorption, and systemic iron overload.[11] At the molecular level, loss of SEC23B function impairs glycosylation, affecting BMP/SMADs signalling and directly influencing hepatic iron hemostasis.[12] Effective management of iron overload is crucial for CDA type 2 patients requiring blood transfusions. Optimal outcomes are achieved through a collaborative approach, emphasizing guidance, support, and thorough information for patients and their families. Interventions like splenectomy and cholecystectomy may be considered, requiring coordination among primary care physicians, haematologists, general surgeons, specialized nurses, and psychologists. Initiation of medical care includes regular blood transfusions and routine monitoring for iron overload every two to three weeks. Our patient with congenital dyserythropoietic anemia received a multidisciplinary approach for management and follow-up care. Although rare in Pakistan, the case involved standard interventions, including bone marrow biopsy for diagnosis. Gaucher disease was initially considered.[13] Given the uncommon occurrence in the region, the team plans for splenectomy and cholecystectomy as part of the optimal management strategy. Therefore, patient counseling on the disease's nature and management is integral. Interferon alpha, effective for CDA type 1, is being considered as a potential treatment for congenital dyserythropoietic anaemia type 2.[14]

CONCLUSION

In summary, when faced with a child who exhibits hepatosplenomegaly, extramedullary hematopoiesis symptoms, erythroid hyperplasia, dyserythropoiesis, or persistent anaemia in bone marrow aspirate studies, it is necessary to consider the possibility of congenital dyserythropoietic anaemia in the differentials. While a thorough examination of bone marrow aspirate & peripheral blood smear analyses is crucial for an accurate diagnosis. Nevertheless, our medical team emphasizes the importance of genetic analysis to determine the definitive treatment for this condition.

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